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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Although there are established standards of care for acute SCI, these vary across trauma centers, and there are in fact very few evidence-based studies of SCI critical care to provide solid guidance for the many treatment decisions facing the SCI care team. In short, even the best teams do not know what the best practices are. We are in critical need of more information about the physiology of acute SCI, the variety of critical care treatments and strategies employed by different practitioners, and how these variables may relate to long-term functional outcomes and QoL, especially with respect to bladder and autonomic functions and their relationship to infection. ***Our objective*** *is to provide a comprehensive prospective analysis of multiple variables in acute SCI impacting long-term outcomes. The three core hypotheses are* **1.** *Multiple critical care variables will be predictive of both sensory-motor and autonomic outcomes, and infection susceptibility at 6&12 mos after SCI.* **2.** *Quantitative MRI of cord damage, and biomarkers of acute immune responses to injury will predict neurological outcomes at discharge and at 6&12 mos.* **3.** *Advanced analytics will yield novel predictors of outcome that will facilitate subsequent clinical trials.*

15. SUBJECT TERMS
Spinal cord injury, acute care, Autonomic, Sensorimotor, MR imaging, outcomes.

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1 **INTRODUCTION:** This project is a prospective observational study of early critical care practices and predictors of outcome in acute spinal cord injury (SCI) conducted at the UCSF campus at the Zuckerberg San Francisco General Hospital and Trauma Center and at the UCSF Fresno Medical Center. Using NINDS SCI common data elements (CDEs) and a custom RedCap database we are collecting detailed physiological, imaging, and treatment data on every enrollable SCI admission to these two level 1 trauma centers. Our objective is to provide a comprehensive prospective analysis of multiple variables in acute SCI that impact long-term outcomes. Participants receive follow-up interviews and ISNCSCI /ASIA neurological scores and classification at 6 and 12 months. Critical care variables include surgical timing and procedure, ICU management and physiological monitoring of blood pressure, pharmacological treatments, and all variables listed in the NINDS CDEs, with special attention to cardiovascular and autonomic variables. High resolution MR imaging is paired with a 'tool kit' of post-processing procedures that will be combined with physiological, genomic, and treatment variables to produce predictive prognostic models. Guidelines based on best practices identified during the study will be communicated to both the military and civilian SCI patient care communities.

2 **KEYWORDS:** Spinal Cord Injury, Acute care, Autonomic, Sensorimotor, MR imaging, outcomes.

3 **ACCOMPLISHMENTS:**

What were the major goals of the project?

Goal 1: Building a knowledge network for acute SCI.

Goal 2: Develop multidimensional prognostic indicators for predicting outcomes and stratifying patients using physiological, imaging and genetic datasets.

Goal 3: Data analysis and sharing.

What was accomplished under these goals? Goal 1. Under this goal we proposed 4 major tasks. The first task was to establish the team. This has been done at ZSFG, and we continue to have biweekly investigator meetings; we have established a continuing agenda to keep focus and to record progress on each of the principle agenda items. The personnel from the second site at Fresno joins the conferences remotely. Now, at the end of year 1, the UCSF Fresno team is fully in place. The second task is to establish the human subjects protocols. The ZSFG protocols have been written and approved by the local committees, have been submitted to the DoD; HRPO approval was received. The UCSF-Fresno site has submitted their protocol to the local committees and was approved, and we have submitted the protocol to the DoD and have obtained HRPO approval for the Fresno site. Task 3 involves implementation of data acquisition protocols.

Currently at ZSFG, we have 21 subjects (6 female, 15 male) with the following characteristics: 1) mean age = 58.4 (range 20-89); 2) spinal cord injuries at the cervical (n=19) and thoracic (n=2) levels; 3) ASIA impairment scores at admission were A (n=3), B (n=2), C (n=1), D (n=7), unable to assess (e.g. comatose, drug impaired, etc) (n=8); 4) mechanism of injury was assault (n=2), fall (n=10), transport (n=6), and sports/leisure (n=1), blunt injury (n=18), penetrating (n=3), central cord cases (n=6); 5) concurrent traumatic brain injury (n=7); 6) mean pre-hospital transport time was 19.6 min (range 3-37 min, n=14); 7) total time in the ER was 351.59 min (range 61-1355 minutes, N= 17); 8) mean time to OR was 15.4 hours (range 1.5-66.2 hrs, N=14); 9) mean hospital stay was 15.88 days (range 2.64-63.8 days, N =15). Subjects were discharged to acute rehab unit (n=9), another hospital (n = 7), home (n=2), deceased (n =1). Some three month follow-up assessments have been completed (n=10), and six month follow ups (n=2). At UCSF/Fresno our second site, enrollment includes 14 subjects (3 female, 11 male) with the following characteristics: 1) mean age = 39.7 (range 19-73); 2) spinal cord injuries at the cervical (n=7), thoracic (n=6) and lumbar (n = 1) levels; 3) ASIA

impairment scores at admission were A (n=5), C (n=1), D (n=2); 4) mechanism of injury was assault (n=4), fall (n=6), transport (n=4), blunt injury (n = 5), penetrating injury (n =5); 6) central cord cases (n=1); 7) concurrent traumatic brain injury (n=2); 8) mean pre-hospital transport time was 12.6 min (range 4-20 min, n=5); 9) mean time in the ER was 277.2 minutes (48-742, n = 9); 10) mean hospital stay was 13.1 days (range 2.9-29.2 days, n = 9); 11) Subjects were discharged to acute rehab unit (n=5), other hospital (n=1), and private residence (n=1). Some three-month follow-up assessments have been completed (n=3). This prospective study is well underway and we expect to be able to continue to accrue patients for the rest of the grant period. Thus, in combination with the prospective cohort from the prior funding period (SC120259), our prospective dataset includes a total of 75 enrolled participants.

In addition, work has commenced to access and refine a number of data types including the physiological monitoring in the OR and ICU, including motor and sensory evoked potentials, the EMS and ER records, and work on the imaging protocols. Dr. Jason Talbott, MD, PhD (OQC, Department of Radiology) has implemented the Spinal Cord Toolbox (SCT), an open-source library of analysis tools for multi-parametric MRI of the spinal cord at UCSF. Initial study was performed to develop and validate a semi-automated image processing and analysis pipeline for axial T2-w MRI images obtained at the time of acute spinal cord injury (SCI). More than 500 texture-features were extracted for 29 acute SCI patients from our retrospective cohort, using atlas-based regions-of-interests. Five machine learning algorithms were explored to determine accuracy for predicting neurologic injury severity. Machine learning algorithms were able to accurately classify patients based on T2w texture features. This is the first study to investigate spinal cord texture features with patient clinical outcomes in spinal trauma. These data show promise for computer-aided prognosis of SCI pathology and will be submitted to the ISMRM 2018 conference. Other data analytic development includes topological data analysis for the proposed multidimensional analysis. We were able to finish a retrospective cohort study to evaluate the proof-of-concept of our novel non-linear multivariate analytical workflow. The core part of this analytical workflow consists of applying non-linear principal component analysis (NL-PCA), a novel approach in the field of SCI. NL-PCA is a specialized type of statistical machine learning tool that can handle data on multiple scales: categorical, ordinal, or interval in a single multidimensional model. NL-PCA achieves this by combining logistic-link approaches similar to RASCH analysis with the power of classic multidimensional pattern detectors like principal component analysis (see Haefeli et al, 2016). Other novel analytics now being developed under the direction of Dr. Jason Talbott, uses a resampled elastic-net regression algorithm which identified top volumetric and texture features of MRIs of the SCI lesions in our prospective dataset. Tissue damage to 1) the white matter was found to be particularly associated with degree of neurological impairment ($p = 0.03$), and 2) ventral gray matter ($p = 0.02$). Inverse variance of SCI lesions was also found to be associated with neurological impairment. Several clinical factors related to associated injury, respiratory, and cardiovascular health were found to be associated with newly derived biomarkers and AIS grade during hospitalization; these included Glasgow coma scale, injury severity score, respiratory failure, mean arterial pressure, systolic blood pressure and vasopressors used in ICU. Due to the fact that clinical and MRI features are correlated and supervene from the same mechanism, severity of spinal cord trauma, modeling was conducted based on vectors of covariance rather than independent variables to predict outcomes. Multivariate regression using components from nonlinear principal component analysis showed high predictive validity for these novel quantitative biomarkers when covariance with other clinical factors is removed. Furthermore, when combined with standard qualitative metrics used to assess lesions, the addition of these new quantitative outcomes improves modeling of neurological impairments.

Another aspect of this goal is to develop genetic biomarkers of injury. This aspect of the project is being performed by Dr. Nikos Kyritsis under Dr. Beattie's supervision. The laboratory procedures for establishing blood collection and RNA preparation have been worked out. Blood collected from 3 uninjured volunteers and 5 de-identified SCI patients, was used for an initial library preparation. Total RNA was extracted from isolated total immune cells of 8 blood samples (3 controls & 5 SCI patient samples). 1 µg of each sample was used to generate DNA libraries for RNA-seq by using the Illumina TruSeq Stranded Total RNA with Ribo-Zero Globin kit. The libraries were pooled together and sent to the Center for Advanced Technology at UCSF for RNA-sequencing using the Illumina HiSeq 4000 platform. The depth was about 35 million reads per sample. The first data show a clear separation between controls vs SCI (see figure 1). Next we started analyzing the raw data. Initially we mapped all the reads against the human genome. All of our samples displayed excellent 'mapability' and show that from a technical perspective the RNA-seq workflow yields good results. Now that the pipeline is established the next step is to send RNA samples from an additional 25 patients and 7 controls; this will occur shortly. Then we will begin our statistical analysis. This aspect of the project is progressing nicely.

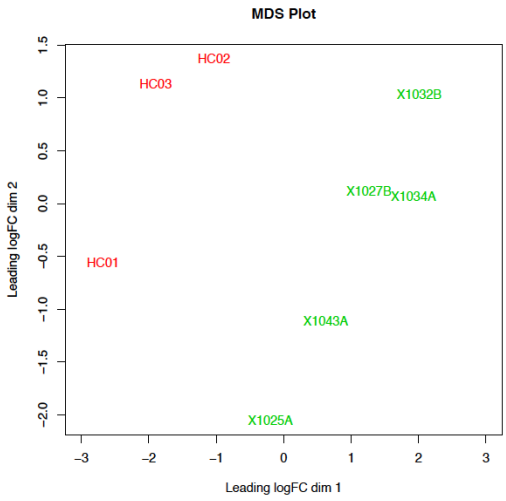

Fig. 1. *Multidimensional plot of individual samples. The plot shows that the Healthy Control samples (red) are clearly different from the SCI patient samples (green) in terms of average gene expression changes. Although the separation between the two groups is obvious, the variation within the groups is also noted.*

Goal 3. Data Analysis and sharing. Data analysis is ongoing and a number of papers and abstracts using the data as it is being accrued have been prepared (see publication list below). We are continuing to refine and improve our data acquisition.

What opportunities for training and professional development has the project provided? The project is being conducted in the setting of a multidisciplinary translational research and training center (BASIC) with the participation medical students, residents, and fellows, and postdoctoral trainees. Thus, while funding for this project is not aimed specifically at training, the resulting infrastructure and database inevitably impact junior trainees. For example, the MRI plus clinical outcomes data are being used by a masters of public health student (David McCoy) to develop advanced analytics for predictive outcomes- a major goal of the project. Dr. Nikolaos Kyritsis is partially supported by this project and he is expert, but still in training, on advanced genomic analysis using RNAseq. Other postdoctoral level professionals have also been involved and published papers in TRACK-SCI (e.g. Dr. Jenny Haefeli) and medical students and residents are collaborating on the project (at no cost). The first two CRCs supported by our DoD awards for TRACK-SCI have received on-the-job training in clinical research, and have both gone on to enter medical school. Finally, the award does provide some funding for conference attendance where TRACK-SCI investigators both present data and receive information.

How were the results disseminated to communities of interest? In addition to full length publications and abstracts and presentation for professional meetings (see below), TRACK-SCI members have reached out this past year to multiple SCI care communities (including UCSF Fresno, Santa Clara Valley Medical Center, Stanford School of Medicine, UC Davis Neurosurgery, UCSF

Marin Neurosurgery) giving grand rounds and advising on our developing critical care guidelines for SCI.

What do you plan to do during the next reporting period to accomplish the goals? All three of our main goals will be worked on. In the next year we will continue to recruit participants at both UCSF/ZSFG and at UCSF Fresno. We will continue to develop data acquisition and analysis methods. For example, we are working on automated analysis of continuous physiological monitoring streams collected from the ICU on our Moberg units. We are continuously upgrading our RedCap data definitions and adding new variables as their importance becomes known- this iterative approach to database development is in anticipation of later clinical trials in which outcome data will be strictly predetermined.

4 IMPACT:

What was the impact on the development of the principal discipline(s) of the project? While we are at an early point in the project, we believe that we are contributing to improving clinical practice for acute care of SCI patients by focusing on MAP goals throughout the early period after SCI, developing MRI analytical tools for predicting outcome after SCI, and potentially developing genetic markers for predicting outcome after SCI. In addition, we are providing the practice guidelines established at BASIC to other sites.

What was the impact on other disciplines and technology transfer? As noted above, we are at an early point in the project and will wait to explicate this as we proceed. But we believe that new analytical tools that are being developed for data analytic as well as image analysis will have impact on the field of Neuroscience as well as clinical areas such as Radiology.

What was the impact on society beyond science and technology? As noted above, we are at an early point in the project and will wait to explicate this as we proceed. But we believe that better early care of people suffering spinal cord injuries will improve their outcome, reduce the burden of disease and increase their productivity so they can better contribute to society at large**.**

5 CHANGES/PROBLEMS:

Changes in approach and reasons for change. Nothing to report; the project is moving forward well.

Actual or anticipated problems or delays and actions or plans to resolve them. Nothing to report.

Changes that had a significant impact on expenditures. Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents Nothing to report

Significant changes in use or care of human subjects Nothing to report.

Significant changes in use or care of vertebrate animals. N/A

Significant changes in use of biohazards and/or select agents N/A

6 PRODUCTS:

Publications, conference papers, and presentations:

Journal publications.

1) Haefeli J, Mabray MC, Whetstone WD, Dhall SS, Pan JZ, Upadhyayula P, Manley GT, Bresnahan JC, Beattie MS, Ferguson AR, Talbott JF. Multivariate Analysis of MRI Biomarkers for Predicting Neurologic Impairment in Cervical Spinal Cord Injury. Am J Neuroradiol. 2016 Dec 22. PMID: 28007771

2) Mabray MC, Talbott JF, Whetstone WD, Dhall SS, Phillips DB, Pan JZ, Manley GT, Bresnahan JC, Beattie MS, Haefeli J, Ferguson AR (2016). Multidimensional analysis of MRI predicts early impairment in thoracic and thoracolumbar spinal cord injury. J Neurotrauma, 33; 954-962. PMCID: PMC4876497

3) Dhall SS, Haefeli J, Talbott JF, Ferguson AR, Readdy WR, Bresnahan JC, Beattie MS, Pan JC, Manley GT, Whetstone W. (2017) Motor Evoked Potentials Correlate With Magnetic Resonance Imaging and Early Recovery After Acute Spinal Cord Injury. Neurosurgy, doi: 10.1093/neuros/nyx320.

4) DiGiorgio AM, Tsolinas R, Alazzeh M, Haefeli J, Talbott JF, Ferguson AR, Bresnahan JC, Beattie GT, Whetsotene WD, Mummaneni PV, Dhall SS (2017) Early chemical DVT prophylaxis after SCI is safe and effective: Pilot Prospective Data. Journal of Neurosurgery Focus, in press.

Books or other non-periodical, one-time publications. None to report.

Other publications, conference papers, and presentations:
1) Haefeli J, Torres D, Ehsanian R, McKenna SL, Suen CG, Nielson JL, Talbott JF, Manley GT, Whetstone WD, Dhall SS, Bresnahan JC, Beattie MS, Pan JZ, Ferguson AR (2016) Operating room autonomic measures as predictors of neurological outcome after spinal cord injury. Abstract, International Spinal Cord Society Meeting, Vienna, Austria.

2) Joseph Graterol, Maria Beylin, Ashleigh Matzoll, Rennie Burke, William Whetstone, Jason Talbott, Robert M. Rodriguez (2017) Yields of paired ordering head and cervical spine CT in blunt trauma patients. Abstract, Society Academic Emergency Medicine Western Regional Meeting.

3) Pascual L, Huie JR, Whetstone WD, Dhall SS, Tsolinas R, Manley GT, Bresnahan JC, Beattie MS, Ferguson AR, Talbott JT (2017) Prospective Determination of Clinical Neurologic Level of Injury with Early MRI Following Blunt Traumatic SCI. Abstract, American Academy of Physical Medicine and Rehabilitation Annual Meeting, October, 2017, PM&R Journal, in press.

4) Singh V, Huie JR, Torres D, Ferguson A, Beattie M, Bresnahan JC, Pan J, Pascual L, Talbott J, Tsolinas R, Fernandez X, Whetstone W, Dhall S, Weinstein P. (2018) Hypotensive Episodes Early After SCI Associated with lower MAP in ICU: A Prospective TRACK-SCI Study. Abstract, Society for Critical Care Medicine Annual Meeting, Submitted.

5) McCoy DB, Dupont SM, Cohen-Adad J, Whetstone WD, Beattie MS, Bresnahan JC, Wilson M, Manley GT, Ferguson AR, Talbott JF (2017) Atlas-Based MRI Texture Feature Analysis Pipeline with Integrated Machine Learning Algorithms Can Predict Neurologic Impairment in Acute Spinal Cord Injury. American Roentgen Ray Society Annual Meeting, submitted.

6) Kyritsis N, Tsolinas R, Duong-Fernandez X, Phillips D, Pan J, Pascual L, Talbott J, Singh V, Whetstone W, Huie J, Manley G, Dhall S, Ferguson A, Bresnahan J, Beattie M, TRACK-SCI Investigators (2017) Using RNAseq to discover blood biomarkers for diagnosis of SCI severity and/or prognosis of neurological recovery: TRACK-SCI. International Symposium for Neural Regeneration, abstract submitted.

- **Website(s) or other Internet site(s)** None to report.
- **Inventions, patent applications, and/or licenses** None to report.
- **Other Products** None to report.

7 PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?** See table below.

Name:	**Michael S. Beattie, PhD**
Project Role:	Principle Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	He oversees the project and its organization and is responsible for all reporting and communications with the sponsor.
Funding Support:	N/A
Name:	**Sanjay Dhall, MD**
Project Role:	Co- Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	He is Director of Spinal Neurotrauma at UCSF/ZSFG, and leads the clinical team in caring for SCI patients and TRACK-SCI subjects.
Funding Support:	N/A
Name:	**Adam R. Ferguson, PhD**
Project Role:	Co- Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	He is head of the Neuroinformatics Core at BASIC and an expert in statistics and multivariate analysis. He has been instrumental in establishing our current RedCap TRACK-SCI database, and is also an investigator on the TRACK-TBI project.
Funding Support:	N/A
Name:	**Jason Talbott, MD, PhD**
Project Role:	He serve as the Optional Qualified Collaborator (OQC)*. He is responsible for evaluating all MR mages for the project, for ensuring that quality controlled data are entered into the RedCap database (with access coded to the secure imaging repository at UCSF), and for processing images through the second tier SCI imaging pipeline.
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Funding Support:	N/A
Name:	**William Whetstone, MD**
Project Role:	He is Professor of Emergency Medicine at UCSF with a main appointment at ZSFG. He has a long history of both preclinical and clinical spinal cord injury research, and is a critical member of the SCI clinical research team.
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Funding Support:	N/A

Name:	**Rachel Tsolinas**
Project Role:	She was the Clinical Research Coordinator for SCI at BASIC/ZSFG, reporting to Drs. Beattie and Dhall. She was responsible for coordinating each new subject's data collection, and processing blood samples in preparation for analysis by the clinical immunology lab and the BASIC labs. She kept track of all records, and communications with the UCSF/ZSFG, UCSF Fresno, and DoD Human Subjects review panels. She left the project for medical school at the end of June.
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Funding Support:	N/A
Name:	**Xuan Duong-Fernandez**
Project Role:	She is the Clinical Research Coordinator for SCI at BASIC/ZSFG, reporting to Drs. Beattie and Dhall. She replaced Rachel Tsolinas.
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Funding Support:	N/A
Name:	**Rebekah Garcia**
Project Role:	Fresno Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Funding Support:	N/A
Name:	**Nikos Kyritsis, PhD**
Project Role:	Post-doctoral Fellow
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	5
Contribution to Project:	He provides laboratory support for the preparation of DNA and RNA and RNA libraries for RNAseq, and will coordinate project needs with the CAT and SABRE cores at UCSF.
Funding Support:	N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to report.

What other organizations were involved as partners?

Organization Name: UCSF Fresno is our second patient accrual site.

Location of Organization: Fresno, CA

Partner's contribution to the project: UCSF Fresno is our second patient accrual site.

SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** N/A
- **QUAD CHARTS:** ***If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.***

JOURNAL OF NEUROTRAUMA 33:954–962 (May 15, 2016)

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Multidimensional Analysis of Magnetic Resonance Imaging Predicts Early Impairment in Thoracic and Thoracolumbar Spinal Cord Injury

Marc C. Mabray,[1] Jason F. Talbott,[1,5] William D. Whetstone,[2,5] Sanjay S. Dhall,[3,5] David B. Phillips,[3,5] Jonathan Z. Pan,[4,5] Geoffrey T. Manley,[3,5] Jacqueline C. Bresnahan,[3,5] Michael S. Beattie,[3,5] Jenny Haefeli,[3,5] and Adam R. Ferguson[3,5,6]

Abstract

Literature examining magnetic resonance imaging (MRI) in acute spinal cord injury (SCI) has focused on cervical SCI. Reproducible systems have been developed for MRI-based grading; however, it is unclear how they apply to thoracic SCI. Our hypothesis is that MRI measures will group as coherent multivariate principal component (PC) ensembles, and that distinct PCs and individual variables will show discriminant validity for predicting early impairment in thoracic SCI. We undertook a retrospective cohort study of 25 patients with acute thoracic SCI who underwent MRI on admission and had American Spinal Injury Association Impairment Scale (AIS) assessment at hospital discharge. Imaging variables of axial grade, sagittal grade, length of injury, thoracolumbar injury classification system (TLICS), maximum canal compromise (MCC), and maximum spinal cord compression (MSCC) were collected. We performed an analytical workflow to detect multivariate PC patterns followed by explicit hypothesis testing to predict AIS at discharge. All imaging variables loaded positively on PC1 (64.3% of variance), which was highly related to AIS at discharge. MCC, MSCC, and TLICS also loaded positively on PC2 (22.7% of variance), while variables concerning cord signal abnormality loaded negatively on PC2. PC2 was highly related to the patient undergoing surgical decompression. Variables of signal abnormality were all negatively correlated with AIS at discharge with the highest level of correlation for axial grade as assessed with the Brain and Spinal Injury Center (BASIC) score. A multiple variable model identified BASIC as the only statistically significant predictor of AIS at discharge, signifying that BASIC best captured the variance in AIS within our study population. Our study provides evidence of convergent validity, construct validity, and clinical predictive validity for the sampled MRI measures of SCI when applied in acute thoracic and thoracolumbar SCI.

Key words: BASIC; MRI; spinal cord injury; thoracic; T2 hyperintensity; TLICS

Introduction

Acute traumatic spinal cord injury (SCI) involving the thoracic and thoracolumbar spinal cord is considerably less common than cervical SCI with approximately 10% of SCI involving the thoracic spine and another 6% involving the cervicothoracic or thoracolumbar junctions.[1] Most of the literature examining MRI findings in acute traumatic SCI have focused on the more common injury to the cervical spinal cord with relatively little attention given to acute SCI caudal to the cervical level.[2–23] Anatomic and functional distinctions are significant between the cervical and more caudal spinal cord segments, suggesting imaging evaluation may, in fact, be level specific.[24,25]

Since the widespread adoption of magnetic resonance imaging (MRI) in evaluating the spinal cord in the acute setting, there have been numerous studies examining the prognostic value of MRI in acute cervical spinal cord trauma.[2–5,7,9,11–23,26,27] The majority of these studies have focused on the longitudinal extent of T2 signal abnormality in the sagittal plane or secondary markers of SCI, such as canal and spinal cord compression in the cervical spine.[2,3,5,7,9,11–23,26–29] The internal architecture of the spinal cord, however, including the predominant longitudinal orientation of functionally important ascending and descending white matter tracts, would suggest that the transverse extent of injury should be a strong predictor of clinical outcome; this hypothesis has been corroborated by pre-clinical and, more recently, human studies.[4,8,30–35]

Departments of [1]Radiology and Biomedical Imaging, [2]Emergency Medicine, [3]Neurological Surgery, and [4]Anesthesia and Perioperative Care, University of California San Francisco and San Francisco General Hospital, San Francisco, California.
[5]Brain and Spinal Injury Center, San Francisco General Hospital, San Francisco, California.
[6]San Francisco Veteran's Affairs Medical Center, San Francisco, California.

A number of reproducible systems have been developed for MRI-based grading in acute SCI. The most recent addition is a grading system for the axial plane, termed the Brain and Spinal Injury Center (BASIC) score.[4] The BASIC score can be used in combination with other measures, including a commonly used sagittal grading system, the longitudinal extent of T2 signal abnormality, maximum canal compromise (MCC), maximum spinal cord compression (MSCC), and the thoracolumbar injury classification system (TLICS). With the exception of TLICS, these injury classification systems were initially developed for the more common cervical SCI but could have prognostic value throughout the spinal axis. In this study, we aim to evaluate the application of the various MRI grading systems in the setting of acute thoracic SCI.

We applied multidimensional data-driven analytics to the full set of imaging classifications to assess validity of these MRI metrics for thoracic SCI. Our hypothesis is that the BASIC score and the other MRI measures of SCI will group together as coherent multivariate principal component (PC) ensembles, and that distinct PCs (PC1, PC2, etc.) will show discriminant validity for predicting distinct impairment patterns in thoracic and thoracolumbar SCI at the time of patient discharge.

To test this hypothesis, we performed an analytical workflow of data-driven discovery to detect multivariate PC patterns followed by explicit hypothesis testing of whether the PCs and the individual MRI measures predict neurologic impairment at discharge. Multidimensional data-driven analytics (i.e., nonlinear PC analysis [NLPCA]) were applied to explore the multivariate clustering among various MRI measures to determine their convergent validity and discriminant validity.

Linear mixed modeling (LMM) was then applied to assess the relationship of these ensemble MRI measures with the degree of neurologic impairment measured by the American Spinal Injury Association (ASIA) Impairment Scale (AIS) at hospital discharge.[36,37] The results provide evidence of face validity, convergent validity, discriminant validity, construct validity, and clinical predictive validity for multiple MRI measures when applied in acute thoracic SCI.

Methods

Study cohort

We performed an Institutional Review Board and Health Insurance Portability and Accountability Act compliant retrospective cohort study evaluating patients who presented to a Level I trauma center between 2005 and 2012 with acute thoracic or thoracolumbar SCI. Patients were identified using a Department of Neurological Surgery database compiled of patients with a principal diagnosis of SCI (International Classification of Diseases codes 952–957).

Inclusion criteria were: (1) age ≥18 years, (2) thoracic and/or lumbar spine MRI including at minimum sagittal and axial T2 imaging, and (3) documented clinical assessments including AIS at admission and discharge. Exclusion criteria were (1) surgical decompression and/or fusion before MRI, (2) MRI that was too degraded by motion or other artifact such that images were nondiagnostic as assessed by an attending neuroradiologist, (3) cervical spinal cord injury, and (4) injuries primarily involving the conus medullaris or cauda equina nerve roots, (5) pre-existing hardware.

Twenty-five patients met inclusion and exclusion criteria. Clinical data collected included patient age, sex, AIS grade at discharge, time to MRI, time to discharge, mechanism, and whether surgical decompression was performed before hospital discharge (Table 1). All patients in the study cohort had a principal diagnosis of SCI and underwent our institutional SCI treatment protocol. The five patients classified as AIS grade E on formal admission examination had documented symptoms of truncal/lower extremity sensory deficits and/or had documentation of motor weakness in the field. These deficits had resolved AT neurological examination on admission and therefore qualify as AIS grade E.

MRI

All MRI were acquired on a 1.5 Tesla GE Genesis Signa HDxt scanner, software version 15 (GE Healthcare, Milwaukee, WI). Routine trauma protocol thoracic spine MRIs were performed including at minimum sagittal T1 and T2 fast spin echo (FSE) sequences and axial T2 FSE sequences. For sagittal T1 imaging, the following parameters were used: slice thickness = 3 mm; time to repetition (TR) = between 520 msec and 630 msec; time to echo (TE) = between 9 msec and 15 msec; echo train length (ETL) = 3; field-of-view (FOV) = 30 cm^2; acquisition matrix = 512 × 512. For sagittal T2: slice thickness, FOV, and matrix size were as above with TR between 3100 msec and 4000 msec and TE between 105 msec and 120 msec; ETL was between 19 and 21. For axial T2 imaging, slice thickness was 4 mm, TR between 4000 and 4800 msec, TE between 102 and 120 msec, ETL = 25, FOV = 18 cm, and acquisition matrix size = 512 × 512. Additional sequences were performed but not evaluated for the purposes of this study.

Image analysis

A board certified neuroradiologist and a neuroradiology trainee performed independent imaging ratings (Table 2), blinded to clinical outcomes, on retrospectively evaluated imaging sequences (Fig. 1). Any disagreements in categorization were discussed with ultimate deferral to the more experienced reader. The level of injury was defined as the epicenter of largest anterior to posterior extent of

Table 1. Patient Characteristics*

Characteristics	
Age (years)	38.32 ± 15.74
Sex	17 male: 8 female
Injury type	Blunt = 21, penetrating = 4
AIS at admission	A = 11, B = 2, C = 1, D = 6, E = 5
AIS at discharge	A = 9, B = 0, C = 2, D = 5, E = 9
Time to MRI (hours)	14.68 ± 18.56
Time to discharge (days)	20.96 ± 21.48
Surgical decompression before discharge	Yes = 16, No = 9
Mechanism of injury	10 fall from height, 5 motor vehicle collision, 3 crush injuries by large falling objects, 2 gunshot wounds, 2 stab wounds, 1 motorcycle collision
Vertebral body level of epicenter of injury by imaging	1 T2, 1 T3, 1 T4, 3 T6, 2 T7, 3 T8, 2 T9, 1 T11, 7 T12, 3 T1, 1 without detectable injury
BASIC score	1.88 ± 1.67
Sagittal grade	2.32 ± 1.22
Longitudinal extent of injury (mm)	23.52 ± 26.56
TLICS Score	5.16 ± 2.78
MCC (%)	23.38 ± 27.36
MSCC (%)	18.67 ± 24.02

*Results are expressed as N or mean ± standard deviation.

AIS, American Spinal Injury Association (ASIA) Impairment Scale; MRI, magnetic resonance imaging; BASIC, Brain and Spinal Injury Center; TLICS, thoracolumbar injury classification system; MCC, maximum canal compromise; MSCC, maximum spinal cord compression.

Table 2. Magnetic Resonance Imaging Scoring Schemes

Brain and Spinal Injury Center grading system	Ordinal	0–4; 0 = normal, 1 = gray matter only, 2 = some WM, 3 = all WM in plane, 4 = with hemorrhage.
Sagittal grade	Ordinal	1–4; 1 = normal, 2 = less than a vertebral body (VB), 3 = longer than one VB, 4 = with hemorrhage
Longitudinal extent of T2 signal abnormality	Numerical	(mm)
Thoracolumbar injury classification system	Ordinal	Rates: morphology (1–4), neurologic status (0–3), and integrity of the posterior ligamentous complex (0–3)
Maximum canal compromise (MCC)	Numerical	MCC (%) = 1−[Dx/(Da+Db)/2] × 100%; D: canal width
Maximum spinal cord compression (MSCC)	Numerical	MSCC (%) = 1−[dx/(da+db)/2] × 100%; d: spinal cord width

cord signal abnormality on sagittal imaging or as the level of bony injury/canal compromise if there was no cord signal abnormality.

BASIC grading was performed as has been described previously (Fig. 1D) by reviewing the axial images at the epicenter of the injury: briefly, grade 0 injury represented normal spinal cord T2 signal, grade 1 injury represented T2 hyperintensity approximately confined to expected location of spinal gray matter, grade 2 injury represented T2 hyperintensity extending beyond the expected margins of central gray matter and obscuring gray-white margins but not involving the entire transverse extent of the spinal cord (a peripheral rim of normal appearing white matter was identified), grade 3 injury represented T2 hyperintensity involving the entire transverse extent of the spinal cord without any residual normal appearing white matter, and grade 4 injury represented grade 3 injury with superimposed discrete foci of intramedullary T2 hypointensity attributed to the presence of macroscopic intramedullary hemorrhage.[4]

All BASIC scoring was based on a single axial image from the injury epicenter that was determined to have the most severe grade among all axial slices. Sagittal grade was assigned as follows (Fig. 1E): grade 1 represented normal spinal cord signal; grade 2 represented T2 hyperintense intramedullary signal with longitudinal extent confined to a single vertebral level; grade 3 represented >1 vertebral level edema; and grade 4 represented mixed hemorrhage and edema.[2,3]

We also measured the greatest longitudinal extent of injury on sagittal T2 images in mm as described in the SCI common data elements (CDE) version 1.0 (Fig. 1A). MCC and MSCC were also both measured on midsagittal images as described previously, by dividing the anterior-posterior (AP) diameter of the canal (for MCC) and the AP diameter of spinal cord (for MSCC) by the average of the canal or spinal cord above and below as described in the literature with MCC measured on T1 and MSCC measured on T2 (Fig. 1B,C).[11,19,27,29,38] TLICS was assigned as described in the literature after reviewing any necessary computed tomography (CT) imaging and the clinical chart.[39–41]

Multidimensional analytical workflow and statistical analysis

All statistical analyses were performed in SPSS v. 22 (SPSS Inc.; Chicago, IL). To assess the relationship between the different MRI measures, we used a NL-PCA in the general workflow depicted in

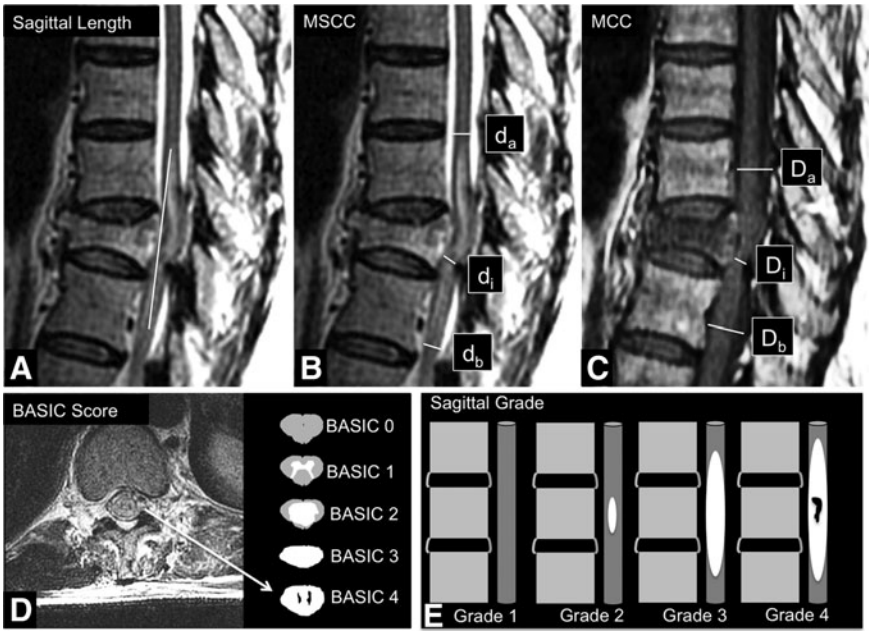

FIG. 1. Image analysis. (**A, B**) Sagittal T2-weighted magnetic resonance imaging (MRI) of the thoracic spine in a patient with acute SCI demonstrating how this sequence was used to measure the length of T2 signal hyperintensity in mm (white line in A) and tocalculate maximum spinal cord compression (MSCC) (B, (1-(d/((da+db)/2)) ×100%). (**C**) Sagittal T1-weighted image of the thoracic spine demonstrating how this sequence was used to measure MCC ((1-(D/((Da+Db)/2)) ×100%). (**D**) Axial T2-weighted MRI of the thoracic spine at the level of the epicenter of injury in a different patient. Foci of T2 hypointense hemorrhage are surrounded by hyperintense edema with no normal cord signal, consistent with BASIC grade 4; white arrow denotes associated cartoon depiction of Brain and Spinal Injury Center (BASIC) axial grade. (**E**) Cartoon of the sagittal grading system.

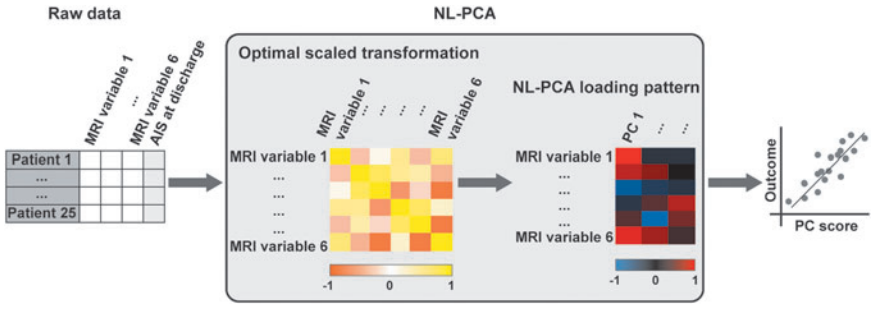

FIG. 2. Multidimensional analytical workflow. Raw magnetic resonance imaging (MRI) variables are fed into a nonlinear principal component analysis (NL-PCA). NL-PCA uses a process called optimal scaling transformation to handle different analysis levels (e.g., ordinal and numeric) in the dataset. Optimal scaling assigns quantitative values to categorical variables optimally, meaning maximizing the variance of the predefined number of principal components (PCs) (i.e., dimensions). The NL-PCA loading pattern shows the weight (i.e., loading) of every single MRI variable on the extracted PCs. In a next step, individual PC scores are used to define the predictive nature of PCs on outcome. An individual PC score is the sum of the multiplied loadings by the individual raw value of every single variable. AIS, American Spinal Injury Association (ASIA) Impairment Scale. Color image is available online at www.liebertpub.com/neu

Figure 2. NL-PCA is suitable for a set of variables including mixed measurement levels (nominal, ordinal, and numeric).[42,43] In NL-PCA, variables are assigned numerical values through an automated process called optimal scaling transformation. First, NL-PCA was applied using a six-dimensional solution. The final dimensionality (i.e., number of PCs) of the PCA was defined based on (1) Kaiser rule: eigenvalue >1 and (2), Cattell rule: scree plot.[44,45] The NL-PCA was then pruned with reduced PC dimensions.

To determine the stability of the NL-PCA solution, we performed a nonparametric balanced bootstrapping procedure using 2000 iterations and Procrustes rotation.[46] The two-dimensional NL-PCA solution was further cross-validated with the bootstrapped solution by using root mean square difference in PC loading patterns, the coefficient of congruence, the Pearson product moment correlation coefficient, and the Cattell salient variable similarity index. Convergence of these mathematically distinct metrics indicates consensus for replication of PC patterns.

The sensitivity of the extracted two-dimensional PC scores for predicting AIS at discharge was tested with a linear mixed model. To assess the bivariate relationship between AIS at discharge and MRI measures, separate Spearman rank correlations and an optimal scaled regression were applied. These procedures allow a direct comparison between the univariate correlations from individual variables and multivariable sets with different metric features (i.e., ordinal and numeric).

All predictive validity testing was based on individual MRI measures from MRI obtained near time of admission and AIS at time of patient discharge from the hospital. Statistical significance for all analysis was set at $\alpha = 0.05$. Bootstrapping and power calculations indicated that the $N = 25$ was sufficient for assessing the predictive validity of MRI with respect to AIS at discharge.

Levels of validity

Validation of MRI measures involves different levels of validity assessment as described by classical measurement theory. ''Face validity'' is defined as the concept that the MRI measures accurately reflect what they purport to measure on face value (i.e., an MRI-measured lesion looks like a lesion). ''Convergent validity'' is the concept that measures that should correlate, do indeed correlate (i.e., lesion length and lesion area do correlate). ''Discriminant validity'' refers to the concept that measures that should diverge, do indeed diverge (i.e., measures of ligamentous change diverge from neuroanatomical measures). ''Construct validity'' refers to the concept that multidimensional patterns are coherent from a theoretical perspective (i.e., neuroscores coalesce as coherent unit). Construct validity can be considered to involve both discriminant and convergent validity. ''Predictive validity'' refers to the concept that multidimensional MRI patterns can predict outcome. In the Results section, we address which level of validity is addressed by each statistical finding.

Results

Patient characteristics, MRI metrics, and TLICS scores for our cohort are presented in Table 1. Optimally scaled correlation revealed strong bivariate associations among MRI measures (Fig. 3A). NL-PCA analysis revealed that PC1–3 had high loadings by MRI scores (Fig. 3B). The Cattell and Kaiser criteria for PC retention converged on retention of a pruned two-dimensional PC solution (Fig. 3C). Re-extraction of NL-PCA restricted to two dimensions confirmed that PC1–2 accounted for 87.0% of the variance (64.3% and 22.7%, respectively) in imaging findings (Fig. 3D).

The bootstrapping results support the stability of the two-dimensional PCA solutions with only marginal changes in the total variance accounted for (total: 89.4%; PC1: 64.3%; PC2: 25.1%). Further, the loading pattern of the two-dimensional NL-PCA strongly agrees with the loading pattern of the bootstrapped PCA solution for both PC1 (root mean square difference = 0, coefficient of congruence = 1, Pearson product moment correlation coefficient = 1, and Cattell salient variable similarity index = 1, $p < 0.05$) and PC2 (root mean square difference = 0, coefficient of congruence = 1, Pearson product moment correlation coefficient = 1, and Cattell salient variable similarity index = 0.86, $p < 0.05$).

In the two-dimensional NL-PCA solution, all imaging variables loaded positively on PC1. MCC, MSCC, and TLICS also loaded positively on PC2 (variance orthogonal to PC1) while BASIC, sagittal grade, and longitudinal extent of injury loaded negatively on PC2. Together these results suggest that the PC1–2 reflect radiological tissue changes (face validity); that PC1 reflects agreement among MRI scoring schemes (convergent validity); and that PC1 and PC2 reflect distinct patterns, with PC2 reflecting divergence among two distinct blocks of scoring schemes (discriminant validity).

To better understand the discriminant nature of PC2, we projected individual patients into the PC1–PC2 biplot space (Fig. 4) and discovered that there appeared to be a broad dispersion of subjects within the PC space, suggesting the potential for distinct subpopulations. We hypothesized that spinal decompression surgery may account for the dissociations among patient distributions. Linear mixed model regression confirmed that spinal decompression

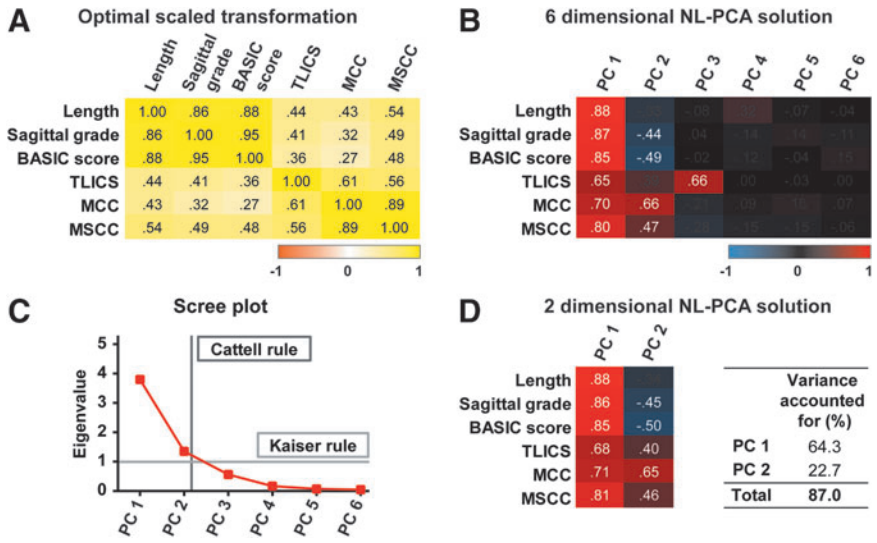

FIG. 3. Non-linear principal component analysis (NL-PCA) results demonstrate face validity, convergent validity, and construct validity. (**A**) Optimal scaled transformation matrix of all magnetic resonance imaging measures. (**B**) Six-dimensional NL-PCA solution loading patterns. Loadings $\geq|0.4|$ are emphasized in white. (**C**) Shows the scree plot for the six-dimensional NL-PCA. The Cattell and the Kaiser rules were applied to define the amount of components to retain for the final NL-PCA. The criteria converged on a two-dimensional solution, (**D**) Shows the re-extracted two-dimensional NL-PCA solution and the amount of variance accounted for by the two principal components (PCs). Loading values $\geq|0.4|$ are in white text. BASIC score, Brain and Spinal Injury Center score; TLICS, thoracolumbar injury classification system; MCC, maximum canal compromise; MSCC, maximum spinal cord compression. Color image is available online at www.liebertpub.com/neu

impacted PC2 scores ($F=25.4$, $p<0.0001$) but not PC1 ($p>0.05$). This suggests that PC2 may reflect MRI features associated with the clinical decision making process to perform spinal cord decompression. Careful re-examination of the loadings further supports this idea (Fig. 3D).

To test the predictive validity of PC1 and PC2 MRI ensembles, we used mixed model regression to test their association with AIS at discharge. Both PC1 and PC2 were statistically significantly related to AIS at discharge (PC1: $F=8.63$, $p=0.001$, eta squared $=0.55$, power $=0.98$; PC2: $F=3.28$, $p=0.041$, eta squared $=0.32$, power $=0.66$). PC1 specifically predicted AIS neurological impairment at time of patient discharge across the range of injuries in a monotonic fashion, with higher PC1 scores reflecting worse function (AIS A) and lower PC1 scores reflecting better function (AIS E) ($p<0.05$ by linear contrast; $p>0.05$ for quadratic).

PC2, on the other hand, had a narrower range of association with neurologic impairment, differentiating AIS A from other AIS grades ($p<0.05$) with no other statistical significance. Because of the retrospective nature of the study, AIS at discharge was chosen as the short-term outcome. To assess the relationship between PC1/PC2 and length of stay, a Pearson correlation was performed (PC1: Pearson $r=0.45$, $p=0.023$, and PC2 $r=-0.39$, $p=0.057$); this indicates that multidimensional MRI predicts length of stay, as a secondary validation end point.

To better understand the predictive validity of the individual MRI scores versus the PC1 and PC2 ensembles, we performed a nonparametric Spearman rank correlations of imaging variables with AIS at discharge (Table 3 and Fig. 5). BASIC score (rho $=-0.93$), sagittal grade (rho $=-0.85$), longitudinal extent of injury (rho $=-0.83$), and PC1 (rho $=-0.75$) were all negatively correlated with AIS at discharge. PC2 (rho $=0.49$) was mildly positively correlated with AIS at discharge, while TLICS, MCC, and MSCC were not statistically significantly correlated with AIS at discharge.

To confirm the comparative predictive validity results, we used an optimal scaled regression. This method provides a way to compare correlations between variables with different properties and distributions. BASIC was the only statistically significant ($p=0.001$) predictor of AIS at discharge in this multiple variable model. Because of multicolinearity, PC1 and PC2 were not included in the optimal scaling regression.

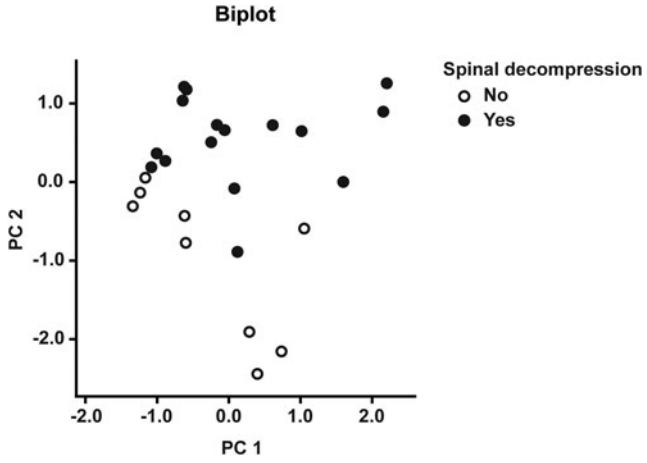

FIG. 4. Discriminant validity of principal component 2 (PC2). Individual subject's PC scores are plotted into the two-dimensional biplot space described by PC1 and PC2. Subjects who underwent surgical decompression (closed circles) after magnetic resonance imaging acquisition have higher PC2 scores than those who did not (open circles). The biplot highlights the discriminative validity of PC2.

Discussion

In this study, we assessed multiple MRI metrics of SCI, which were all predominately developed for use in the more common cervical SCI, here applied in thoracic SCI. TLICS, which is an

Table 3. Spearman Rank Correlation and Optimal Scaling Regression to Predict American Spinal Injury Association (ASIA) Impairment Scale at Discharge*

	Spearman correlation			*Optimal scaling regression*			
	Rho	*Rho squared*	*Sig*	*Zero-order*	*Partial*	*Part*	*Sig*
Length	–0.83	0.68	<0.001	–0.81	–0.09	–0.02	0.859
Sagittal grade	–0.85	0.73	<0.001	–0.67	0.65	0.16	0.514
BASIC score	–0.93	0.86	<0.001	–0.96	–0.92	–0.44	0.001
TLICS	–0.21	0.04	0.323	–0.11	–0.64	–0.15	0.203
MCC	–0.04	0.00	0.850	–0.17	0.30	0.06	0.405
MSCC	–0.20	0.04	0.351	–0.40	0.06	0.01	0.862
PC1	–0.75	0.57	<0.001				
PC2	0.49	0.24	0.014				

*Length of signal abnormality, sagittal grade, Brain and Spinal Injury Center (BASIC) score, and principal component (PC)1 are all negatively correlated with AIS at discharge while PC2 is positively correlated with American Spinal Injury Association (ASIA) Impairment Scale (AIS) at discharge. Optimal scaling regression identified BASIC score as the only statistically significant variable in this multiple variable model to predict AIS at discharge.

TLICS, thoracolumbar injury classification system; MCC, maximum canal compromise; MSCC, maximum spinal cord compression.

injury classification system for surgical decision making in thoracic spinal column injury and not a prognostic system, was also included to evaluate its relationship with the other imaging variables. TLICS does incorporate clinical data related to patient neurologic status in addition to imaging findings.

We used nonlinear principal components analysis to characterize the relationships of these variables and found two PCs accounting for 87.0% of the variance. All imaging variables loaded positively on PC1 (64.3% of the variance), which was highly related to AIS at discharge. MCC, MSCC, and TLICS also loaded positively on PC2 (22.7% of the variance), while variables concerning spinal cord signal abnormality loaded negatively on PC2. We found that PC2 was highly related to the patient undergoing surgical decompression.

BASIC, sagittal grade, and longitudinal extent of signal abnormality were all negatively correlated with AIS at discharge with the highest individual level of correlation for BASIC. In a multiple variable model, BASIC was the only statistically significant predictor of AIS at discharge, demonstrating that it most accurately predicted the variance of AIS at discharge in our study population. Our study provides evidence of convergent validity, construct validity, and clinical predictive validity for these imaging predominant measures of SCI when applied in acute thoracic SCI.

Variables involving spinal cord signal abnormality are highly related to each other and to AIS at discharge. By definition, these three variables are similar because they primarily consider the presence or absence of T2 signal hyperintensity in the spinal cord. The axial grading system (BASIC) and the sagittal grading system differ in their mild to moderate grades and direction of significance; however, both consider hemorrhage superimposed on edema as the highest grade. Otherwise, in the mild to moderate grades, BASIC is primarily concerned with the degree of spared white matter and the sagittal grading system is primarily concerned with single vertebral level versus multiple vertebral level edema. The sagittal grading

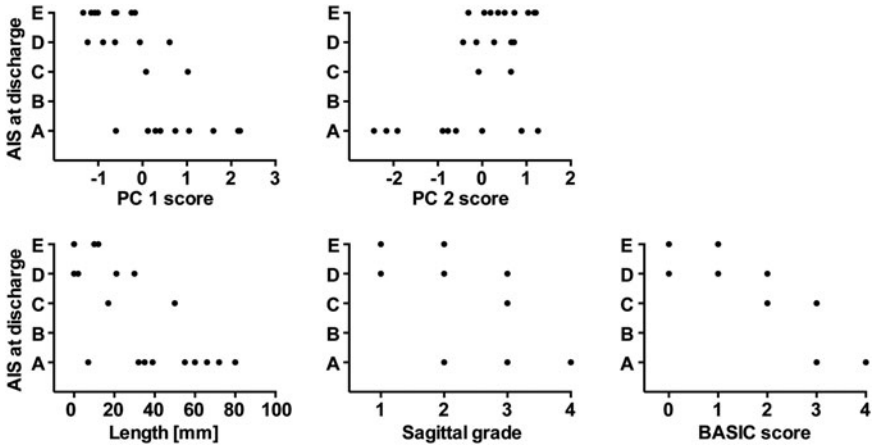

FIG. 5. Predictive validity. Scatterplots of American Spinal Injury Association (ASIA) Impairment Scale (AIS) at discharge with each statistically significant variable. Brain and Spinal Injury Center (BASIC) score had the highest individual level of individual correlation with AIS at discharge. BASIC score (rho = –0.927), sagittal grade (rho = –0.852), longitudinal extent of injury (rho = –0.825), and principal component (PC)1 (rho = –0.753) were all negatively correlated with AIS at discharge. PC2 (rho = 0.486) was mildly positively correlated with AIS at discharge, while thoracolumbar injury classification system, maximum canal compromise, and maximum spinal cord compression were not statistically significantly correlated with AIS at discharge. Note that because of the ordinal scale of the sagittal grade and the BASIC score, a number of subjects coincide on both x and y axes.

system (ordinal) and the longitudinal extent of T2 signal abnormality (numerical) are by definition similar concepts except that the sagittal grade also accounts for the presence of hemorrhage.

As expected, these variables grouped together on PC analysis and were positively correlated together providing evidence of convergent and construct validity and were negatively correlated with AIS at discharge providing evidence of clinical predictive validity. BASIC demonstrated the highest individual degree of negative correlation with AIS at discharge; however, all three metrics can be considered individually valid for predicting early neurological impairment in thoracic SCI.

The multiple variable model identified BASIC as the dominant imaging variable in predicting AIS at discharge, because it was the only statistically significant variable in the multiple regression model. This suggests that BASIC (a brief ordinal scale) most tightly captures AIS (also a brief ordinal scale) at discharge compared with the other measures.

MCC, MSCC, and TLICS grouped together with the other imaging variables on PC1 but diverged from the other imaging variables (of spinal cord signal abnormality) on PC2. Because PC2 was highly related to the patient undergoing spinal decompression and positively correlated with AIS at discharge, the relationship of these variables that loaded positively on PC2 (MCC, MSCC, TLICS) with AIS at discharge is thus quite complex. These three variables have variance with PC1 correlating negatively with AIS at discharge, and variance with PC2 correlating positively with AIS at discharge and being highly related to the likelihood of undergoing surgical decompression.

PC2 thus may capture some of the nuances of surgical decision-making reflected in TLICS whereby an incomplete SCI at admission receives a higher individual scoring than a complete SCI. The particular phenotype captured by a high PC2 score would be a patient with a high MCC, MSCC, and TLICS but lower scores on measures of cord signal abnormality; a patient with an unstable spine and compression but a relatively preserved spinal cord.

The fact that MCC and MSCC did not individually have a significant correlation with AIS at discharge is consistent with previous literature examining measures of spinal canal stenosis with thoracolumbar SCI outcomes and may reflect the complexity of their relationship with both surgical decision making and subsequent early neurological impairment.[47] The strong negative correlations between direct MRI measures of SCI (BASIC score, sagittal grade, and longitudinal length of T2 signal hyperintensity) and clinical outcomes suggests incorporation of these measures into surgical decision-making tools may be helpful. Defining valid imaging biomarkers for thoracic and thoracolumbar SCI is critically important because the thoracic spinal cord has been proposed as the most suitable region for initial invasive clinical trials targeting SCI.[48,49]

Our study has several limitations mostly related to the retrospective technique and relatively small sample size. Our retrospective technique allowed us to effectively study the relatively rare thoracic SCI in an efficient manner but did limit the clinical variables to those already collected in routine clinical care. The retrospective nature of this study also limits our control over timing of MRI after injury.

Leypold and colleagues[50] have shown that the longitudinal extent of T2 hyperintensity can increase by up to one vertebral body height per day in the acute stage of injury. Our institution routinely obtains MRI early after injury, and 88% (22/25) were performed within 24 h of injury, thus limiting the effect of delayed timing on extent of T2 hyperintensity. Future prospective controlled experiments would ideally control for variables such as hemodynamic support, timing of surgical decompression, steroid therapy, and timing of MRI after injury with longer-term clinical follow-up and a larger number of patients. Importantly, our study does suggest that any prospective collection of data in thoracic SCI should include metrics of spinal cord signal abnormality on MRI as measured in this study.

Another limiting factor is the use of AIS grade as a fairly coarse primary outcome measure for thoracic SCI in our cohort. Because of the retrospective nature of this study, more granular outcome measures, such as functional independence measure (FIM), were not available for analysis. Although the significance of AIS grade has been questioned in thoracic SCI, Lee and colleagues[51] recently showed that AIS grade changes are associated with significant functional benefit relative to FIM scores and ambulation in a retrospective analysis of a large longitudinal database of patients with thoracic SCI.[52]

Structural MRI findings correlated with early impairment with varying resolution, depending on the scoring scheme (e.g., BASIC vs. sagittal grade). Multiple regression analysis confirmed that most of the univariate MRI assessments were noisy correlates of functional impairment, with the sole exception of the BASIC score. In testing theory, this class of evidence is referred to as predictive validity, and it directly addresses whether a set of measurements (MRI features) have value for predicting a separate outcome domain (AIS grade) at a later time.

Our application of NL-PCA directly assessed whether the multidimensional ensemble of spinal cord MRI features performs better than each individual outcome. NL-PCA is a rigorous and appropriate approach for performing multivariate pattern-detection to compare the relative merits of multiple scales that purport to measure the same underlying features (in this case, structural MRI features). This approach has a long history in physics, human performance testing, and other disciplines dating back more than a century.[53,54]

Although it is currently unusual to have such advanced analytics applied in the clinic, applications like the one here promise to be a central feature of the emerging field of ''precision medicine,'' where analytics will be integrated in clinical decision making.[55,56] Accordingly, several very recent articles incorporate NL-PCA as a precision medicine tool in both pre-clinical and clinical SCI.[57–59] The present findings suggest that multidimensional MRI features of the thoracic spinal cord may have relevance for clinical issues such as patient stratification for diagnosis, intervention planning, and clinical trial criteria. Further work is needed, however, to test the capacity of structural MRI to predict long-term outcome.

Conclusion

This study validates the use of BASIC and other MRI measures of acute SCI specifically in the setting of thoracic SCI. PC analysis identified two distinct patterns of variance: PC1, which was highly related to AIS at discharge, and PC2, which was highly related to surgical decompression. The highest individual correlation with AIS at discharge was seen with the BASIC system, although all metrics of spinal cord signal abnormality had a high degree of individual negative correlation with AIS at discharge. The relationship of MCC and MSCC with AIS at discharge was found to be more complex, likely reflecting the use of these metrics along with TLICS in surgical decision making. A multiple variable regression model identified BASIC as the only statistically significant predictor of AIS at discharge, signifying that BASIC best captured the variance in AIS within our study population.

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Author Disclosure Statement

Dr. Talbott is a member of the data monitoring committee for StemCells, Inc.; Dr. Ferguson is an *ad hoc* consultant for Acorda Therapeutics. For the remaining authors, no competing financial interests exist.

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Multivariate Analysis of MRI Biomarkers for Predicting Neurologic Impairment in Cervical Spinal Cord Injury

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ABSTRACT

BACKGROUND AND PURPOSE: Acute markers of spinal cord injury are essential for both diagnostic and prognostic purposes. The goal of this study was to assess the relationship between early MR imaging biomarkers after acute cervical spinal cord injury and to evaluate their predictive validity of neurologic impairment.

MATERIALS AND METHODS: We performed a retrospective cohort study of 95 patients with acute spinal cord injury and preoperative MR imaging within 24 hours of injury. The American Spinal Injury Association Impairment Scale was used as our primary outcome measure to define neurologic impairment. We assessed several MR imaging features of injury, including axial grade (Brain and Spinal Injury Center score), sagittal grade, length of injury, maximum canal compromise, and maximum spinal cord compression. Data-driven nonlinear principal component analysis was followed by correlation and optimal-scaled multiple variable regression to predict neurologic impairment.

RESULTS: Nonlinear principal component analysis identified 2 clusters of MR imaging variables related to 1) measures of intrinsic cord signal abnormality and 2) measures of extrinsic cord compression. Neurologic impairment was best accounted for by MR imaging measures of intrinsic cord signal abnormality, with axial grade representing the most accurate predictor of short-term impairment, even when correcting for surgical decompression and degree of cord compression.

CONCLUSIONS: This study demonstrates the utility of applying nonlinear principal component analysis for defining the relationship between MR imaging biomarkers in a complex clinical syndrome of cervical spinal cord injury. Of the assessed imaging biomarkers, the intrinsic measures of cord signal abnormality were most predictive of neurologic impairment in acute spinal cord injury, highlighting the value of axial T2 MR imaging.

ABBREVIATIONS: AIS = American Spinal Injury Association Impairment Scale; BASIC = Brain and Spinal Injury Center; MCC = maximum canal compromise; MSCC = maximum spinal cord compression; NL-PCA = nonlinear principal component analysis; PC = principal component; SCI = spinal cord injury

Early biomarkers of spinal cord injury (SCI) are essential during the acute phase of injury, a time when crucial management decisions are made and a period of great prognostic anxiety for patients and families.[1-3] As emerging experimental therapies translate to the clinic, early biomarkers will also be important for patient selection and monitoring in clinical trials. Multiple potential MR imaging biomarkers exist to evaluate acute SCI.[1,4-20] These measures primarily focus on the sagittal imaging plane, examining factors such as length of T2-hyperintense signal within the cord, whether abnormal signal is confined or spans multiple vertebral levels, presence of hemorrhage, and secondary markers of cord injury such as spinal cord compression and spinal canal compromise.[1,5-22] The internal structure of the spinal cord, with predominantly longitudinally oriented WM tracts, suggests that the axial injury extent and WM sparing should also be strong predictors of outcome. This concept has been demonstrated in preclinical studies and recently in human studies introduc-

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ing an axial scoring system known as the Brain and Spinal Injury Center (BASIC) score.[4,23-30] However, until now, it has been unclear how the axial grading relates to other imaging biomarkers of the sagittal plane and extrinsic compression measures.

The various MR imaging–based metrics have been shown to be reproducible, and all have some individual degree of predictive validity for clinical outcome.[1,4-20] Here, we evaluated the relationships of these MR imaging metrics to each other and to neurologic impairment. We applied a data-driven tool, nonlinear principal component analysis (NL-PCA), to understand the relationship between different MR imaging biomarkers and assess their ability to predict neurologic impairment. NL-PCA detects statistical patterns, incorporating multiple variables independent of their scale and decomposing them into a smaller set representing multidimensional clusters of variables (principal components [PCs]) that covary.[31,32] We then used nonlinear regression approaches to benchmark different MR imaging assessments against each other for predicting neurologic impairment at discharge. We hypothesized that MR imaging measures of acute cervical SCI would group together as a coherent multivariate PC ensemble and that distinct PCs (PC1, PC2, etc) would predict neurologic impairment. We intended 1) to provide insight into relationships between early MR imaging biomarkers after acute cervical SCI and 2) to provide an evaluation of the predictive validity of each individual measure of neurologic impairment.

MATERIALS AND METHODS

Study Cohort

This study was HIPAA and institutional review board compliant. We performed a retrospective cohort study of patients with acute blunt cervical SCI evaluated at a Level I trauma center (Zuckerberg San Francisco General Hospital) from 2005 to 2014. Inclusion criteria were 1) blunt acute cervical SCI, 2) age ≥18 years, 3) presurgical cervical spine MR imaging performed within 24 hours after injury, and 4) documented American Spinal Injury Association Impairment Scale (AIS) at both admission and discharge. Exclusion criteria were 1) penetrating SCI, 2) surgical decompression and/or fusion before MR imaging, 3) MR imaging that was too degraded by motion or other artifact such that images were nondiagnostic, and 4) preexisting surgical hardware. Of 212 patients initially identified, 95 patients met all inclusion and exclusion criteria and were included in the study. The data collected included sex and age, AIS at admission and discharge (as documented in the chart and performed by appropriately trained physiatrists and neurosurgeons), hours to MR imaging from time of injury, days to discharge, and whether surgical decompression of the cervical spine was performed before discharge. Fifty-two of the 95 patients included in this study were included in a cohort of patients as part of a previously published study.[4] This prior, smaller study involved initial development and interrater reliability testing of the BASIC score, whereas the current study tests multiple MR imaging grading schemes against each other, and against neurologic outcome, by using multivariate statistical analysis.

MR Imaging

All MR imaging examinations were acquired on the same 1.5T Genesis Signa scanner (GE Healthcare, Milwaukee, Wisconsin). We assessed sagittal T2 FSE, sagittal T1, and axial T2 FSE sequences performed as part of our routine imaging protocol, with these sequences not substantially changing over the study interval. Additional sequences performed as part of our trauma imaging protocol were not evaluated. Sequences were performed with the following parameters (presented as mean ± standard deviation from 10 randomly selected examinations): 1) for axial T2 FSE through the entire cervical spine: TR, 3798 ms ± 586 ms; TE, 102 ms ± 6 ms; section thickness, 3 ms; echo-train length, 17 ± 3.4; in-plane FOV, = 160 × 160 mm with a 512 × 512 matrix for nominal in-plane resolution of 0.31 mm^2; 2) for sagittal T2 FSE: TR, 3585 ms ± 563 ms; TE, 105 ms ± 5 ms; section thickness, 3 mm; echo-train length, 17.1 ± 3; in-plane FOV, 200 × 200 mm; and 3) for sagittal T1: TR, 528 ms ± 103 ms; TE, 16 ms ± 1.3 ms; section thickness, 3 mm; echo-train length, 2.6 ± 0.8; and in-plane FOV, 200 × 200 mm with a 512 × 512 matrix for nominal in-plane resolution of 0.39 mm^2.

Image Analysis

A neuroradiology fellow (M.C.M.) and attending physician (J.F.T.) performed consensus MR imaging ratings for all metrics while blinded to clinical outcome. The interrater reliability and BASIC axial MR imaging grading have been previously described as follows[4,30]: grade 0, no cord signal abnormality; grade 1, T2 hyperintensity confined to GM; grade 2, intramedullary T2 hyperintensity extends beyond expected gray matter margins to involve spinal white matter, but does not involve entire transverse extent of the spinal cord; grade 3, T2 hyperintensity involving GM and some but not all of WM; grade 4, T2 hyperintensity involving the entire axial plane of the spinal cord; grade 5, grade 3 injury with the addition of foci of T2 hypointensity consistent with hemorrhage. Sagittal grading was assigned as previously described: grade 1, no spinal cord signal abnormality; grade 2, single-level T2 hyperintensity; grade 3, >1 vertebral level T2 signal hyperintensity; grade 4, T2 signal hyperintensity with areas of hypointensity representing hemorrhage.[1,19] The greatest length (mm) of injury on sagittal T2 was measured as described in the National Institutes of Health/National Institute of Neurologic Disorders and Stroke SCI common data elements version 1.0.[3] Maximum canal compromise (MCC) and maximum spinal cord compression (MSCC) assessed midsagittal images by dividing the anteroposterior diameter of the canal (on sagittal T1 for MCC) and the anteroposterior diameter of spinal cord (on sagittal T2 for MSCC) by the average of the canal or spinal cord above and below as previously described.[8,15,16,22]

Multidimensional Analysis Workflow and Statistical Analysis

NL-PCA assessed the relationship among MR imaging measures by incorporating pattern detection with optimal-scaling transformations to accommodate nonparametric, ordinal, and nonlinear relationships that are common in clinical assessment tools such as MR imaging scoring by a radiologist.[33,34] Established decision rules defined the final dimensionality: Kaiser rule criterion of eigenvalue >1 and Cattell rule (ie, scree plot).[33-36] Validity of MR imaging and PC scores for predicting AIS at discharge involved linear mixed model, Spearman rank correlation, and an optimal-scaled regression.

Receiver operating characteristic curves assessed sensitivity and specificity of MR imaging measures for predicting AIS at

discharge by using a sliding scale (ie, AIS A versus B, C, D, E; AIS A, B versus C, D, E; AIS A, B, C versus D, E; and AIS A, B, C, D versus E), resulting in 4 separate receiver operating characteristic curves. In addition, we completed a supplementary analysis where we compared adjacent groups. Because of the low number of patients in the AIS B subgroup ($n = 3$), AIS A and B were grouped together as a motor complete group. We compared the areas under the curve of the different MR imaging biomarkers.

In a next step, we used discriminant function analysis to assess within the BASIC measure the optimal combination of scores to discriminate the different AIS groups. BASIC score was recoded as: 1) a simple lesion/no lesion score (BASIC 0 = no lesion, and BASIC 1–4 = any lesion) and 2) into a 3-point scale merging BASIC score subcategories 1–3 into 1 category. All MR imaging variables and the 2 recoded BASIC score variables were fed into a discriminant function analysis test for discrimination of AIS at discharge. Statistical significance for all tests was set at $\alpha = .05$. All statistical analyses were performed in SPSS v.23 (IBM, Armonk, New York). Syndromic plots for the PC loadings were generated in custom-designed software in R (http://www.r-project.org/).[37]

Table 1: Patient characteristics[a]

Age	57.91 ± 18.15
Sex (M, F)	67, 28
AIS at admission	A = 26, B = 9, C = 18, D = 42
AIS at discharge	A = 17, B = 3, C = 15, D = 41, E = 19
Time to MRI (hours)	6.97 ± 5.15
Time to discharge (days)	25.15 ± 35.31
Surgical decompression	Yes = 63, No = 32

[a] Values expressed as *N* or mean ± SD.

Table 2: MRI scoring schemes

BASIC	Ordinal	0–4: 0 = normal; 1 = GM only; 2 = some WM; 3 = all WM in plane; 4 = with hemorrhage
Sagittal grade	Ordinal	1–4: 1 = normal; 2 = less than a VB; 3 = longer than 1 VB; 4 = with hemorrhage
Longitudinal extent of T2 signal abnormality	Numeric	[mm]
MCC	Numeric	MCC % = $1 - \{D_i/[(D_a + D_b)/2]\} \times 100\%$; D = canal width[a]
MSCC	Numeric	MSCC % = $1 - \{d_i/[(d_a + d_b)/2]\} \times 100\%$; d = spinal cord width[a]

Note:—VB indicates vertebral body.
[a] See Fig 1 for further description.

RESULTS

Patient characteristics are listed in Table 1. MR imaging measurements are outlined in Table 2 and Fig 1. The relationships between the BASIC score and AIS at discharge are listed in Table 3. NL-PCA demonstrated all imaging parameters loaded highly on PC1. PC2 discriminated MR imaging measures, with only MSCC and MCC showing high loadings (On-line Fig 1*A*). Statistical decision rules pruned the initial 5-dimensional NL-PCA solution to 2 dimensions (On-line Fig 1*B*). The optimal-scaled transformation matrix revealed a high correlation between the lesion length, sagittal grade, and the BASIC score and, to a lesser extent, between the compression variables (MSCC and MCC) (Fig 2*A*). The loading patterns of the 2-dimensional NL-PCA solution are displayed in Fig 2*B*. PC1–2 accounted for 88.6% of the total variance in the dataset (PC1, 58.6%; PC2, 30%). All imaging variables loaded highly on PC1. Variance explained by PC1 represents convergence across all MR imaging variables. In contrast, PC2 mainly captures compression variables MSCC and MCC, representing divergence of the MR imaging variables of intrinsic cord signal abnormality.

In Fig 2*C*, individual PC scores are projected into PC1 and PC2 space, with each patient color-coded by AIS change and by AIS grade at discharge. Patients with higher scores on the PC1 axes have worse AIS at discharge. Confirming this,

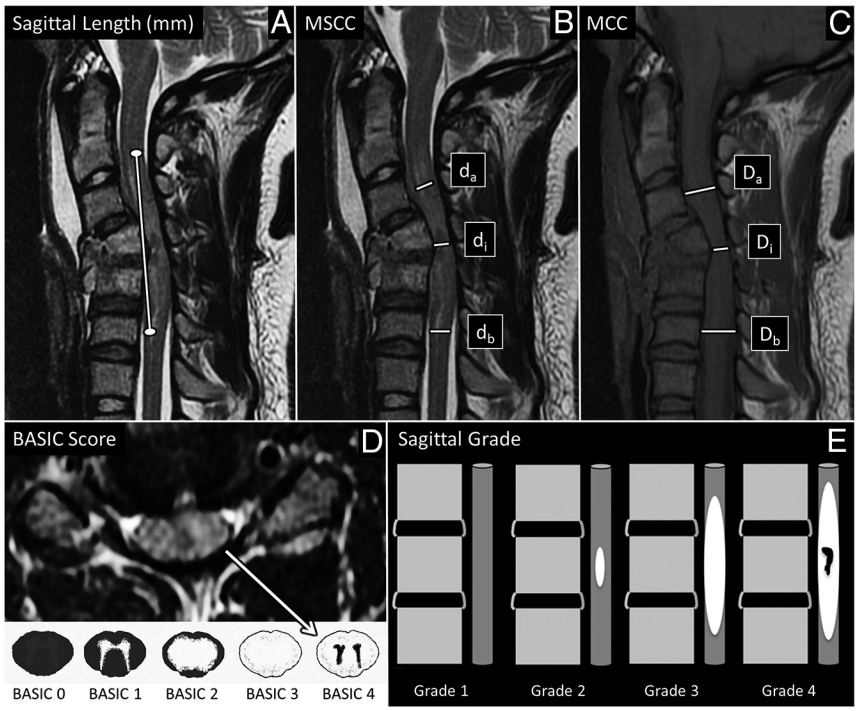

FIG 1. MR imaging-based metrics. *A* and *B*, Sagittal T2-weighted MR imagings of the cervical spine of patients with acute SCI were used to measure the length of T2 signal hyperintensity in mm (*A*, *white line*) and to calculate MSCC (*B*, $1 - \{d_i/[(d_a + d_b)/2]\} \times 100\%$). d_i indicates distance of the spinal cord at the injury site; d_b, one segment below the injury site; d_a, one segment above the injury site. *C*, Sagittal T1-weighted image of the cervical spine demonstrating how we used this sequence to measure MCC ($1 - \{D_i/[(D_a + D_b)/2]\} \times 100\%$). D_i indicates distance of the spinal canal at the injury site; D_b, one segment below the injury site; D_a, one segment above the injury site. *D*, The axial T2-weighted MR imaging of the cervical spine at the level of the epicenter of injury was used to define the BASIC score. Areas of macroscopic T2-hypointense hemorrhage are surrounded by hyperintense edema with no normal cord signal, consistent with BASIC grade 4. BASIC axial grade cartoons are depicted in the *lower panel*. *E*, Shows cartoons of the sagittal grading system. Sag indicates sagittal.

a linear mixed model revealed that PC1, but not PC2, significantly predicted AIS at discharge (PC1: $F = 33.79$, $P < .001$; PC2: $F = 2.11$, $P = .086$).

To compare predictive validity of PC1 and PC2 versus univariate MR imaging measures, we applied univariate nonparametric Spearman rank correlations for prediction of AIS at discharge (Table 4 and Fig 3). Based on Spearman rank correlation, variables of intrinsic cord signal abnormality (lesion length, sagittal grade, BASIC score) and both PC1 and PC2 predicted AIS at discharge. Neither MSCC nor MCC significantly correlated with AIS at discharge. Lesion length ($\rho = -0.66$), sagittal grade ($\rho = -0.70$), BASIC score ($\rho = -0.85$), and PC1 ($\rho = -0.69$) all negatively correlated with AIS at discharge, whereas PC2 showed a weak positive correlation with AIS at discharge ($\rho = 0.22$).

We used optimal-scaled regression to benchmark the predictive validity of MR imaging measures against each other. An advantage of the optimal-scaled regression is that it takes into account different analysis levels (ordinal versus continuous) in a single model. PC scores were not included in this analysis because of multicollinearity. BASIC was the only significant predictor of AIS at discharge ($P < .01$).

We next benchmarked how individual MR imaging measures perform in predicting AIS at discharge compared with AIS at admission. Not surprisingly, AIS at admission showed a strong positive correlation with AIS at discharge by Spearman rank correlation ($\rho = 0.82$, $P < .01$). Optimal-scaling regression revealed that BASIC score and AIS at admission were the only significant predictors of AIS at discharge (both $P < .01$) (On-line Table 1).

We were concerned that BASIC prediction of AIS at discharge may be confounded by the decision to perform surgical decompression, which could also influence outcome. To test this, we performed 2 additional waves of analysis. First, we tested whether BASIC score significantly predicted the decision to perform surgical decompression by using a generalized linear model. BASIC score significantly predicted surgical decompression decision-making (Wald $\chi^2 = 9.00$, $P = .003$). To test whether this confounded BASIC's predictive validity for AIS at discharge, we reran the generalized linear model with an interaction term, testing whether BASIC and surgical decompression were statistically entangled. This analysis maintained the significant predictive main effect of BASIC on AIS (Wald $\chi^2 = 34.92$, $P < .001$). Furthermore, undergoing decompression surgery was not a significant predictor of AIS at discharge (Wald $\chi^2 = 0.17$, $P = .68$), nor was there a significant interaction between BASIC and decompression surgery (Wald $\chi^2 = 1.58$, $P = .66$). Similarly, we wanted to assess if BASIC significantly predicts AIS at discharge after correcting for MSCC. Using the same analysis tools, the predictive validity of BASIC was maintained ($F = 30.69$, $P < .001$), and there was no interaction effect between AIS at discharge and MSCC ($F = 0.79$, $P = .53$).

The sensitivity and specificity (receiver operating characteristic and area under the curve) of the MR imaging

Table 3: BASIC score in relation to AIS at discharge[a]

	AIS A	AIS B	AIS C	AIS D	AIS E	Total Patients
BASIC 0				1 (7.7)	12 (92.3)	13
BASIC 1				12 (70.6)	5 (29.4)	17
BASIC 2		1 (2.6)	10 (25.6)	26 (66.7)	2 (5.1)	39
BASIC 3	7 (43.8)	2 (12.5)	5 (31.3)	2 (12.5)		16
BASIC 4	10 (100)					10

[a] Data presented as no. of patients (%).

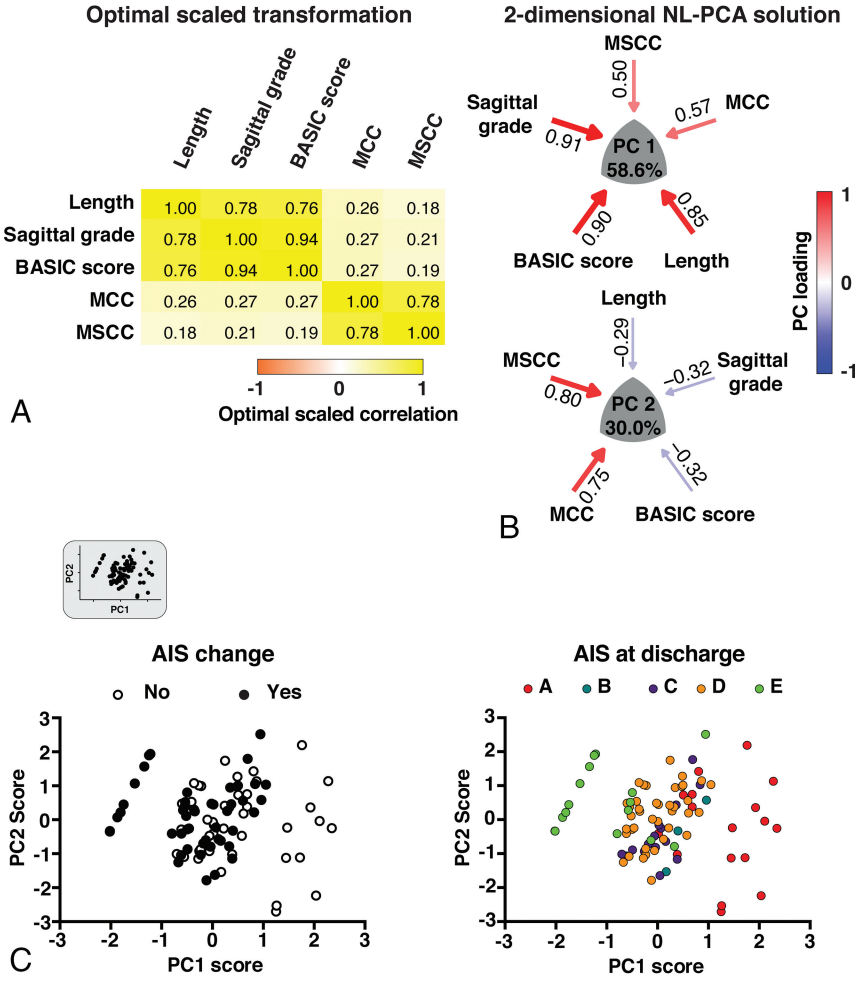

FIG 2. Results of the 2-dimensional NL-PCA. *A*, Heat map of the optimal-scaled transformation matrix of all MR imaging measures included in the NL-PCA. The matrix indicates all bivariate cross-correlations: *yellow* indicates a positive relationship and *orange* indicates a negative relationship. *B*, 2-dimensional NL-PCA solution. PCs reflect the clustered variance shared by the MR imaging measures and are represented by a *convex triangle*. The *arrow gauge* and the intensity of the color (*red* indicates a positive relationship and *blue* indicates a negative relationship) show the magnitude (ie, loading weights) of the correlation between each MR imaging measure and the PC. *C*, Bi-plots of individual patients ($n = 95$) in the 2-dimensional space described by PC1 and PC2. In the *top left corner*, the extracted bi-plot is displayed. In the *left graph*, the same bi-plot is color-coded by AIS change (ie, AIS change from admission to discharge) and is color-coded in the *right graph* by AIS at discharge. PCA indicates principal component analysis.

Table 4: Predicting AIS at discharge—Spearman rank correlation and optimal scaling regression results

	Spearman Correlation			Optimal Scaling Regression			
	ρ	ρ^2	*P* Value	Zero-Order	Partial	Part	*P* Value
Length	−0.66	0.44	<.01	−0.65	−0.11	−0.05	.50
Sagittal grade	−0.70	0.49	<.01	−0.69	0.36	0.18	.10
BASIC score	−0.85	0.72	<.01	−0.87	−0.75	−0.50	<.01
MCC	−0.20	0.04	.05	−0.24	0.02	0.01	.90
MSCC	−0.14	0.02	.18	−0.20	−0.08	−0.04	.62
PC1	−0.69	0.48	<.01				
PC2	0.22	0.05	.03				

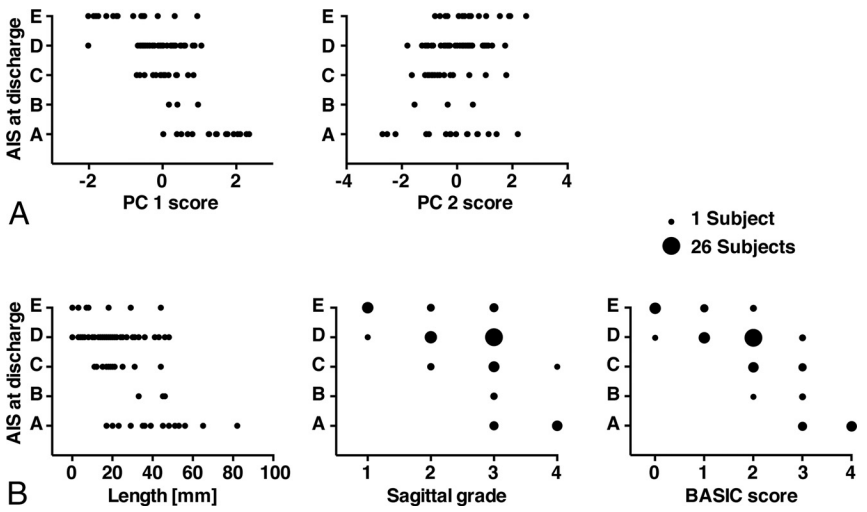

FIG 3. Multivariate (PCs) and univariate prediction of AIS at discharge. *A*, PC1 was negatively correlated with AIS at discharge, and PC2 showed a weak positive correlation. *B*, The length of the lesion, the sagittal grade, and the BASIC score showed a negative correlation with AIS at discharge. Note that because of the ordinal scale of the BASIC score and the sagittal grade, some subjects coincide on the same value. The number of subjects within each sphere is represented by the size of the spheres. Only scatterplots of the statistically significant correlations between the MR imaging measures and AIS at discharge are displayed.

measures in predicting AIS at discharge are shown in Fig 4 (AIS sliding scale). Supporting previous analysis, the length, sagittal grade, and BASIC score predicted AIS at discharge, with their areas under the curve statistically superior to random guessing (Table 5). BASIC consistently had the highest area under the curve in comparison with the other MR imaging measures. In a supplementary analysis, we tested how well the MR imaging measures can discern adjacent AIS categories. The results are shown in On-line Table 2. Similar to the sliding scale results, BASIC consistently had the highest area under the curve for distinguishing both severe and mild AIS categories in comparison with the other MR imaging measures.

Finally, to assess discriminative value score subcategories, we applied a linear discriminant function analysis. This supervised pattern detection approach discovers the optimal combination of scores to discriminate the different AIS groups. The full BASIC score had the largest absolute correlation with the canonical discriminant function for AIS, suggesting that the full 5-point BASIC score performs better than truncated scoring schemes (0.962). The full BASIC score outperformed both the simple dichotomous score (lesion versus no lesion, with BASIC 0 = no lesion and BASIC 1–4 = any lesion; 0.388) and a 3-point scale merging BASIC score subcategories 1–3 into 1 category (BASIC 0 = no lesion, BASIC 1–3 = nonhemorrhagic lesion, BASIC 4 = hemorrhagic lesion; 0.639). A second discriminant function analysis included only patients with a BASIC score of 1–3 (ie, those patients with nonhemorrhagic intramedullary T2 signal abnormality) to define the prognostic value of BASIC in this specific subpopulation. BASIC had the largest absolute correlation with the discriminative function (0.991), followed by the length of the lesion (0.416).

DISCUSSION

We applied data-driven multivariate analytic techniques to evaluate how multiple MR imaging–derived metrics relate to each other and to short-term impairment when applied to a group of 95 patients with acute blunt cervical SCI. We identified 2 principal components (PC1 and PC2) that explained 88.6% of the total variance in the dataset. Measures of intrinsic spinal cord signal abnormality had the highest positive loading on PC1, whereas measures of extrinsic cord compression had more modest positive loading. Both the BASIC score and sagittal grade had greater correlation with outcome than PC1, whereas BASIC score was the only univariate MR imaging measure to correlate with outcome when correcting for differences in data measurement scales. The present results support the prognostic relevance of the BASIC score compared with other MR imaging measures of SCI.

Although all imaging variables loaded positively on PC1, PC2 was more discriminatory in nature, segregating structural measures of compression from variables reflecting intrinsic cord signal abnormality. PC2 had a weakly positive correlation with AIS ($\rho = 0.22$, $P = .03$), whereas measures of extrinsic compression had no significant correlation with outcome. These findings demonstrate the discriminant validity of NL-PCA and highlight the split between MR imaging measures of intrinsic cord signal abnormality and structural measures of compression.[30] Structural measures of compression thus have a complex relationship with outcome. The present data do not necessarily conflict with prior work examining the predictive validity of MSCC in acute SCI.[8,15,16,21,22] Miyanji and colleagues[8] showed that MSCC was a key predictor of neurologic recovery after traumatic SCI. In that study, outcome for patients with SCI was dichotomized into complete and incomplete categories, whereas we have used the more granular 5-point AIS grading scale. In addition, after correcting for baseline neurologic status, only intrinsic measures of SCI significantly correlated with neurologic recovery, findings consistent with the present results.[8]

Receiver operating characteristic analysis confirmed that of the imaging variables examined, the BASIC score was the most accurate for predicting short-term impairment. We were con-

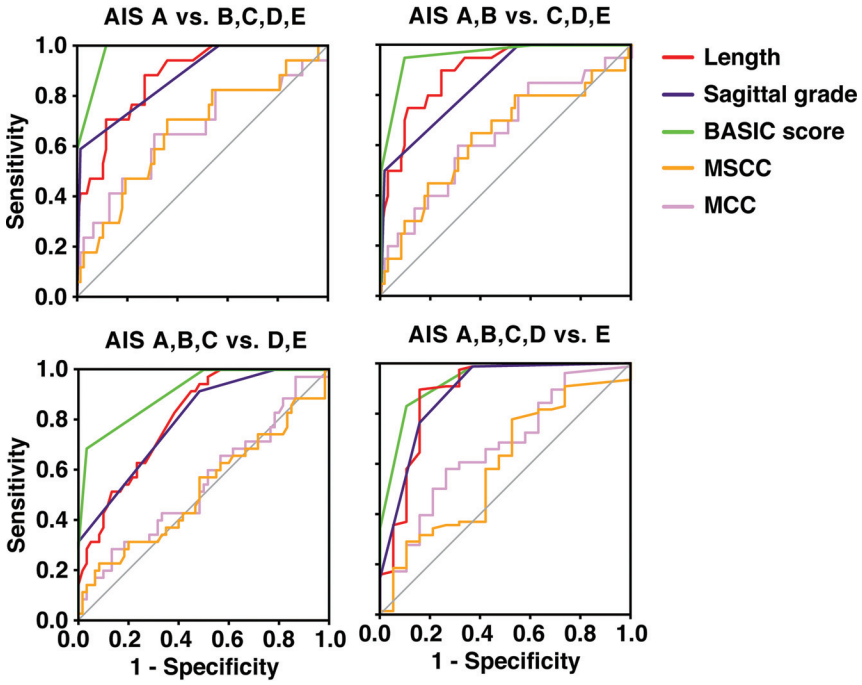

FIG 4. Receiver operating characteristic curves for the different MR imaging measures. The curves show the sensitivity and specificity of the different measures to predict AIS at discharge. AIS at discharge was dichotomized by using a sliding scale, resulting in 4 separate receiver operating characteristic curves (AIS A versus B, C, D, E; AIS A, B versus C, D, E; AIS A, B, C versus D, E; and AIS A, B, C, D versus E). The *diagonal gray line* represents a reference line that corresponds to random guessing. The further the receiver operating characteristic curves are located to the *top left corner*, the higher is the sensitivity and specificity of the measure in predicting the dichotomized AIS at discharge.

Table 5: Receiver operating characteristic analysis results

	AUC	*P* Value	95% CI
AIS A vs. B, C, D, E			
Length	0.88	<.01	0.80–0.96
Sagittal grade	0.88	<.01	0.79–0.97
BASIC score	0.98	<.01	0.95–1.00
MCC	0.66	.039	0.50–0.82
MSCC	0.66	.036	0.51–0.81
AIS A, B vs. C, D, E			
Length	0.90	<.01	0.83–0.97
Sagittal grade	0.86	<.01	0.77–0.94
BASIC score	0.96	<.01	0.92–1.00
MCC	0.65	.05	0.50–0.79
MSCC	0.64	.06	0.49–0.79
AIS A, B, C vs. D, E			
Length	0.81	<.01	0.72–0.89
Sagittal grade	0.80	<.01	0.71–0.89
BASIC score	0.91	<.01	0.85–0.97
MCC	0.55	.44	0.43–0.67
MSCC	0.52	.71	0.40–0.65
AIS A, B, C, D vs. E			
Length	0.88	<.01	0.77–0.99
Sagittal grade	0.88	<.01	0.79–0.98
BASIC score	0.93	<.01	0.86–0.99
MCC	0.66	.03	0.52–0.80
MSCC	0.59	.21	0.45–0.74

Note:—AUC indicates area under the curve.

cerned that other factors may confound the prognostic validity of the BASIC score. For example, the decision to perform surgical decompression may be influenced by the presence and pattern of signal abnormality in the spinal cord, which could influence outcome.[38-40] In addition, the extent of spinal cord compression with associated cord deformation may potentially confound BASIC grading. Our analysis confirms that the predictive validity of the BASIC score was maintained after correcting for potential interactions from surgical decompression and spinal cord compression.

Prior studies suggest MR imaging is most accurate at predicting outcomes when patients have evidence for very mild (normal cord signal) or very severe (intramedullary hemorrhage) injury.[1,6,7,10,13,14,20] In contrast, tremendous variability in clinical outcomes has been described in the setting of intermediate degrees of injury.[1] To specifically evaluate MR imaging measures and outcomes in this subgroup of patients from our cohort, we applied discriminant function analysis to patients with a BASIC score of 1–3 (patients with nonhemorrhagic intramedullary T2 signal hyperintensity; $n = 72$). Even in this subpopulation, the BASIC score had a very high absolute correlation with the discriminant function (0.991), followed by the length of the lesion (0.416). Therefore, the prognostic capabilities of the BASIC score are not simply attributable to the ease of prognosis at the ends of the injury severity spectrum.

Limitations of our study primarily relate to the retrospective, single-institution study design. We are actively pursuing this subject further in a prospective fashion with longer clinical follow-up at multiple time points and more detailed outcome measures. Our technique was designed to look at the relationships of the various imaging metrics to each other and to clinical outcome (AIS at discharge). Although we believe that the current study is adequate for investigating these relationships, we realize that there are changes in neurologic impairment expected over a longer time course. In addition, in a future prospective study, more detailed outcome measures need to be included to more comprehensively capture neurologic function.

CONCLUSIONS

This study demonstrates the utility of applying NL-PCA for defining the relationship between MR imaging biomarkers in a complex clinical syndrome of cervical SCI. Independent, prospective studies are needed to validate our conclusion that intrinsic measures of spinal cord pathology on acute MR imaging, particularly the BASIC score, best predict neurologic impairment in acute SCI compared with measures of extrinsic compression. This analytic pipeline is suited for future patient-level investigation and is amenable to inclusion of emerging potential biomarkers. Multidimensional approaches may also be useful for future prospective validation of imaging metrics

derived from advanced quantitative techniques such as DTI, which are under active investigation for spinal cord pathology.[26,41-43]

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Q2	Author: Please expand the acronym 'IRB', if required.	
Q3	Author: Please provide table captions for 'Table 1' and 'Table 2'.	
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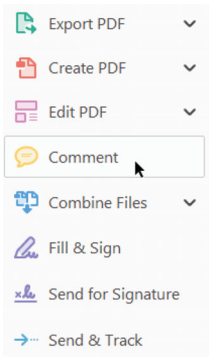

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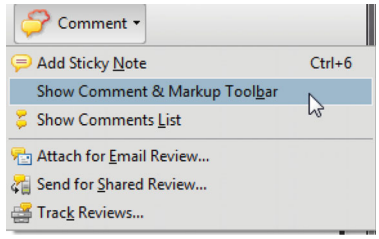

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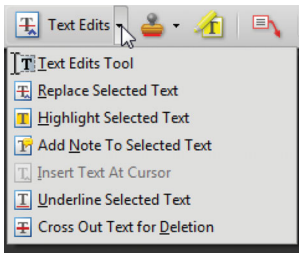

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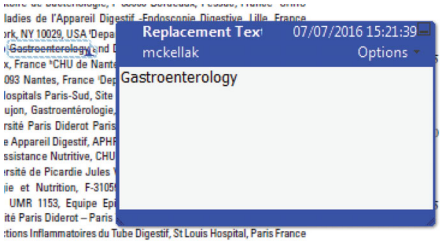

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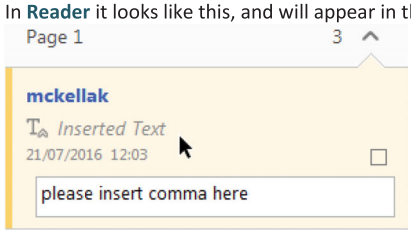

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Motor Evoked Potentials Correlate With Magnetic Resonance Imaging and Early Recovery After Acute Spinal Cord Injury

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BACKGROUND: While the utilization of neurophysiologic intraoperative monitoring with motor evoked potentials (MEPs) has become widespread in surgery for traumatic spine fractures and spinal cord injury (SCI), clinical validation of its diagnostic and therapeutic benefit has been limited.

OBJECTIVE: To describe the use of intraoperative MEP at a large level I trauma center and assess the prognostic capability of this technology.

METHODS: The SCI REDCap database at our institution, a level I trauma center, was queried for acute cervical SCI patients who underwent surgery with intraoperative monitoring between 2005 and 2011, yielding 32 patients. Of these, 23 patients had severe SCI (association impairment scale [AIS] A, B, C). We assessed preoperative and postoperative SCI severity (AIS grade), surgical data, use of steroids, and early magnetic resonance imaging (MRI) findings (preoperatively in 27 patients), including axial T2 MRI grade (Brain and Spinal Injury Center score).

RESULTS: The presence of MEPs significantly predicted AIS at discharge ($P < .001$). In the group of severe SCI (ie, AIS A, B, C) patients with elicitable MEPs, AIS improved by an average of 1.5 grades (median = 1), as compared to the patients without elicitable MEP who improved on average 0.5 grades (median = 0, $P < .05$). In addition, axial MRI grade significantly correlated with MEP status. Patients without MEPs had a significantly higher axial MRI grade in comparison to the patients with MEPs ($P < .001$).

CONCLUSION: In patients with severe SCI, MEPs predicted neurological improvement and correlated with axial MRI grade. These significant findings warrant future prospective studies of MEPs as a prognostic tool in SCI.

KEY WORDS: Spinal cord injury, Evoked potentials, Intraoperative monitoring, BASIC score

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While the utilization of intraoperative neurophysiologic monitoring (IOM) with somatosensoryevoked potentials (SSEP) and motor evoked potentials (MEPs) has become widespread in surgery for traumatic spine fractures and spinal cord injury (SCI), scientific studies of its diagnostic and therapeutic benefit have been limited. Several studies have demonstrated the value of IOM in spinal fusion and deformity, but there have been limited clinical studies documenting the use of IOM in spine trauma.[1,2] In particular, there is a paucity of data addressing the use of MEPs in this population. Given the anatomic basis of SSEPs and MEPs, it is generally accepted that SSEPs are more useful in the identification of posterior and dorsal column damage, while the utility of MEPs extends to the localization of anterior lesions in the motor aspect of the cord.[3,4]

This lack of clinical research is striking given that there is significant literature supporting the prognostic value of early neurophysiologic

ABBREVIATIONS: AIS, association impairment scale; **BASIC,** Brain and Spinal Injury Center; **EMG,** electromyography; **IOM,** intraoperative neurophysiologic monitoring; **MAP,** mean arterial pressure; **MEPs,** motor evoked potentials; **SCI,** spinal cord injury; **SSEPs,** somatosensory evoked potentials; **tcMEPs,** transcranial motor evoked potentials

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monitoring in preclinical models of SCI.[5,6] The few clinical studies that have documented intraoperative MEP use in traumatic spinal injury have not addressed the relationship between MEPs and clinical neurological function or recovery. Curt et al[7] showed a correlation between MEPs and neurological recovery in chronic SCI, but did not investigate the role of IOM, as their acute group received their first MEPs testing an average of 25 d post-trauma. Costa et al[8] found that epidural MEPs (D-waves) during early stabilization at an unclear time after injury were correlated with motor recovery.[8] Other studies have likewise examined the relationship between functional outcomes and MEPs, without examining the role of IOM. How intraoperative electrodiagnostic findings correlate with early imaging findings also remains largely unexplored in the setting of acute SCI.[9,10]

The purpose of this study was (1) to examine the relationship between MEP and clinical exam findings in acute SCI patients, (2) to assess MEPs for prognostic value in acute SCI, and (3) to explore the correlation between MEP and acute magnetic resonance imaging (MRI) findings.

METHODS

Study Design, Setting, and Participants

We performed a retrospective chart review to evaluate the diagnostic and prognostic value of MEPs for acute SCI patients admitted to a level I trauma center, between January 2005 and December 2011. The University IRB approved all research activities and the study was exempted from patient consent as it was classified as minimal risk. Patients were identified using a Department of Neurosurgery REDCap database of all spinal cord injuries/admissions and cross-referencing trauma logs, and searchable terms using electronic medical records. From this database, we retrospectively identified 131 patients with a principal diagnosis of SCI (code 953-957) according to the International Classification of Diseases, ninth revision, clinical modification, from codes designating discharge diagnoses. Of these patients, 32 met inclusion and exclusion criteria. All of these patients were cervical injuries. To be eligible, patients had to (1) be age $\geq$ 18, (2) have undergone surgical decompression utilizing intraoperative MEPs, and (3) have documented American Spinal Injury Association Impairment Scale (AIS) grading performed both at time of admission before surgery, as well as follow-up AIS grading (performed at time of patient discharge from acute care hospital). AIS grading was performed by SCI-trained physiatrists, neurosurgical, and neurocritical care physicians, and was selected as a measure of neurological outcome based on current guidelines for the classification of spinal cord injuries from the American Association of Neurological Surgeons/Congress of Neurological Surgeons.[11-13] AIS grades were obtained on all patients included in this study both before surgery and upon discharge. We excluded patients < 18 yr of age, SCI related to penetrating trauma or imaging evidence for complete spinal cord transection.

Intervention Parameters: Imaging Workup and Initial Management

Twenty-seven patients underwent spine MRI prior to operative stabilization. MRI was performed on a 1.5 Tesla GE Genesis Signa scanner with imaging parameters as previously described (GE Healthcare, Milwaukee, Wisconsin).[14] Axial grading of MRI images was performed as previously described by Talbott et al,[14] utilizing the Brain and Spinal Injury Center (BASIC) score. All grading was performed by an attending neuroradiologist who was blinded to the clinical status of the patients. Briefly, based on the most severely affected axial T2 MRI image at the injury epicenter, grades were assigned as follows: grade 0 injury was defined as no cord signal abnormality, grade 1 injury was defined as T2 hyperintensity approximately confined to the gray matter, grade 2 injury was defined as T2 hyperintensity involving gray and some but not all of the white matter, grade 3 injury was defined as T2 hyperintensity involving the entire axial plane of the spinal cord, and grade 4 injury was defined as grade 3 injury with the addition of foci of T2 hypointensity consistent with macroscopic intramedullary hemorrhage.[14] Five patients were excluded from MRI analysis because they did not have an MRI performed prior to decompressive surgery.

Our institutional spinal cord perfusion clinical protocol was initiated with mean arterial pressure (MAP) goal of greater than 85 mm Hg based on the current recommendations for acute SCI.[15] Earlier in the course of this patient population, high-dose methylprednisolone was used at the discretion of the treating spine surgeon. Reflective of nationwide trends, steroids fell out of favor and were subsequently discontinued due to a lack of benefit and concern for deleterious effects.[16]

Intervention Parameters: Definitive Management

All patients underwent surgical decompression and instrumented stabilization, with a total of 32 surgical procedures in 32 patients. All surgeries were performed with IOM, including baseline MEP and SSEP prior to positioning and surgery.

Intervention Parameters: IOM

Cadwell Cascade Elite neuromonitoring equipment for neurophysiologic monitoring of transcranial electrically stimulated MEPs (tcMEPs), SSEPs, and free-running/evoked electromyography (EMG) were used (Cadwell Inc, Kennewick, Washington). For tcMEP monitoring, subdermal needle electrodes were placed in trapezious, deltoids, biceps, triceps, thenar, hypothenar, and foot flexor/foot extensor muscles bilaterally. Stimulation was carried out using a Cadwell TCS-1 double train stimulator (pulse with 50 ms, 2 trains of a total of 9 pulses, 1.7 ms interstimulus, interval 13.1 ms intertrain interval), constant voltage ranged from 100 to 1000 V. Transcranial stimulation was achieved using subdermal needle electrodes inserted at C1/C2. Anodal stimulation applied to C1 produced muscle responses in right-sided musculature, whereas anodal stimulation applied to C2 produced muscle responses in left-sided musculature. For EMG activity monitoring, subdermal needle electrodes placed for tcMEPs were used for cervical root monitoring bilaterally. A needle electrode in the right shoulder served as a ground. SSEPs/tcMEPs/EMGs were amplified using differential amplifiers (Cadwell Cascade), averaged and computer monitored (Dell, Round Rock, Texas). The anesthesia protocol used was propofol 120 mcg/kg/min, fentanyl 100 mcg/h with Sevoflurane 1.0% (0.5 MAC) and an MAP goal of >85 mm Hg was instituted given any concern for MEP integrity in low dose volatile anesthetics.[17]

Prepositioning baseline measures for both SSEPs and MEPs were established. Postprone position change baseline measures were also obtained. Final readings were taken with quantification/comments on significant changes in SSEPs/tcMEPs from baseline values. Two separate, blinded attending physicians independently evaluated whether MEPs

TABLE 1.

Descriptive demographics Variable[a]	n = 32	MEP absent n = 13	MEP present n = 19
Male	26 (81.25)	10	16
Female	6 (18.75)	3	33
Mean age (yr)	57.4 ± 17.65	49.5 ± 16.6	63.1 ± 16.3 g
Mean MAP goals > 85 (h)	121.78 ± 41.9	135.5 ± 36.4	110.59 ± 43.60
Mean ISS score	22.83 ± 13.27	29.7 ± 16.9	19.4 ± 7.91
Steroids given	19 (59.38)	8	11
No steroids	13 (40.63)	5	8
Mean ICU LOS (d)	15.42 ± 19.39	26 ± 24.5	8.65 ± 5.928
Mean hospital LOS (d)	26.16 ± 26.81	33.92 ± 29.9	20.90 ± 21.45
Mortality	1 (3.33)	1	00

[a]Continuous variables reported as mean ± standard deviation; categorical variables reported as n (percent of total).

were present or absent based on the operating room Neurophysiologist's analysis of signal quality, communication to the surgeon, and reproducibility of waveforms. MEPs with weak signal were considered present as long as they were reproducible with a constant stimulation voltage.

Statistical Methods

All statistical analyses were performed in SPSS v.23 (SPSS Inc, IBM, Armonk, New York). We used a Mann–Whitney *U*-test to assess if early impairment (ie, AIS at discharge) differs between patients that had absent vs present intraoperative MEPs. In a next step, we tested if the amount of recovery in AIS grade is different between the patients with absent MEPs in comparison to the patients with present MEPs, (i) in the entire patient population and (ii) in a subpopulation of more severe SCI patients (ie, AIS A-C) using Mann–Whitney *U*-tests. The subpopulation analysis of the more severe SCI patients was done to address whether MEP analysis might be specifically useful in patients with more severe SCI, as patients having an initial AIS D grade are most likely to have preserved MEPs and have less room on the AIS scale to exhibit recovery (ie, a ceiling effect). Given that within our patient population the time to discharge was variable, we used an independent sample *t*-test to define if the hospital length of stay was different between the patients with absent MEPs in comparison to patients with present MEPs.

We used a Kruskal–Wallis test to assess if early impairment (ie, AIS at discharge) differs between patients having different axial grading of MRI images acquired prior to surgery (ie, BASIC score). In addition, we tested if intraoperative MEPs correlated with the BASIC scores using a Spearman correlation. Statistical significance for all tests was set at $\alpha = 0.05$.

RESULTS

Participants and Descriptive Demographics

The mean age in this cohort of patients was 57.4 (range 22-86 yr) and AIS grades at admission were A (n = 12), B (n = 5), C (n = 6), D (n = 9). Descriptive demographics for this cohort can be found in Table 1. Of note, approximately 19 of the 32 patients received high-dose methylprednisolone. There was no clear relationship between administration of high-dose methylprednisolone and MEPs or AIS recovery. All patients underwent surgical decompression and stabilization with intraoperative MEPs, this decompression occurred within 36 h for all patients.

Main Results

Patient change of AIS grades from admission to hospital discharge can be seen in Table 2. The presence of MEPs significantly predicted AIS at discharge ($P < .001$, Mann–Whitney *U*-test). Namely, patients with present intraoperative MEPs had higher AIS grades at discharge in comparison to patients with absent MEPs. When looking at the entire patient population (ie, initial AIS A-D grades), the amount of recovery in AIS grade was not significantly different between patients with absent MEPs in comparison with patients with present MEPs ($P = .158$, Mann–Whitney *U*-test). However, in the subgroup analysis that included the patients with more severe SCI (ie, AIS A-C), AIS recovery was significantly different between patients with MEPs vs patients without intraoperative MEPs ($P < .05$, Mann–Whitney *U*-test). In the group of severe SCI (ie, AIS A, B, C) patients with elicitable MEPs, AIS improved by an average of 1.5 grades (median = 1), as compared to the patients without elicitable MEP who improved on average 0.5 grades (median = 0). We were concerned that the variable time to discharge within the patient population might have caused this effect. However, the length of hospital stay of subjects with present intraoperative MEPs was not significantly different from the ones with absent MEPs (t [28] = 1.47, $P = .15$). The relationship between the presence and absence of intraoperative MEPs and AIS grade conversion is shown in Figure. All severe SCI patients (AIS A-C) that had present intraoperative MEPs converted at least 1 AIS grade from admission to discharge. In the patient cohort that did not have elicitable intraoperative MEPs (n = 13), 8 did not show any AIS grade conversion and 1 patient deteriorated from AIS B to A. There

TABLE 2.

Variable[a]	Incidence of recovery stratified by initial AIS grade AIS A (n = 12)	AIS B (n = 5)	AIS C (n = 6)	AIS D (n = 9)
1 grade improvement	0 (0)	2 (40.0)	5 (83.33)	3 (33.33)
2 grade improvement	3 (25.0)	1 (20.0)	1 (16.67)	0 (0)
3 grade improvement	1 (8.3)	0 (0)	0 (0)	0 (0)
4 grade improvement	1 (8.3)	0 (0)	0 (0)	0 (0)
No improvement or regression	7 (58.3)	2 (40.0)	0 (0)	6 (66.67)

[a]Categorical data reported as n (percent of total).

COLOUR

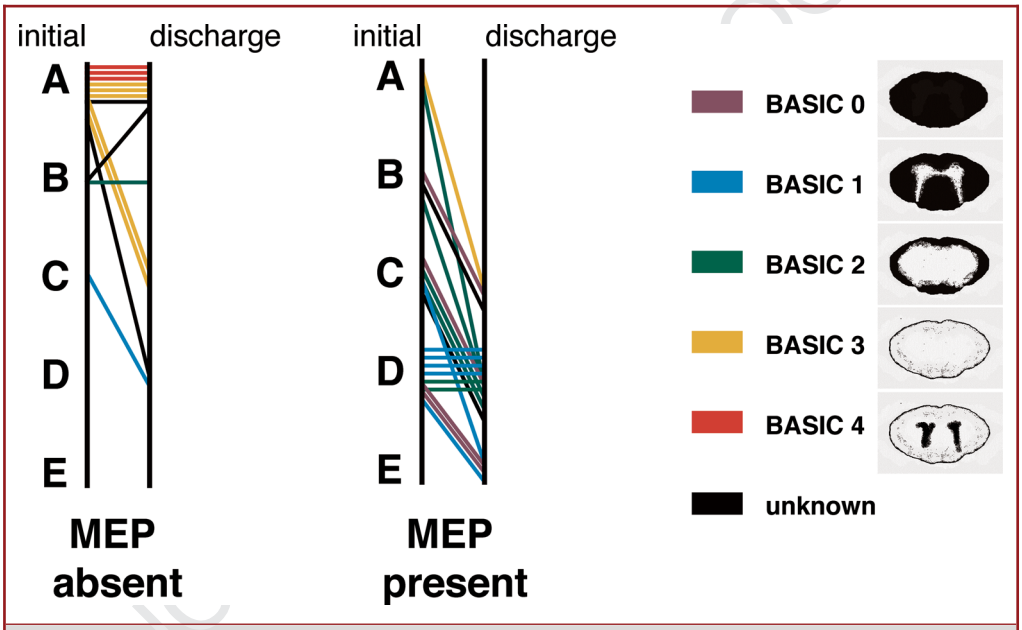

FIGURE. *Change in neurological status by MEP status and axial T2 MRI pattern (BASIC score). Crossover plots for all patients without (left) and with (middle) elicitable MEPs. Each patient on the crossover plots is also color-coded by their axial T2 MRI pattern (legend on far right). A black line indicates that MRI was not performed and axial T2 pattern is therefore unknown.*

was no significant difference in time to surgery for patients with or without MEPs. We then removed all AIS A patients from both groups, and performed another analysis of the remaining AIS B and C patients. Though the resulting group was too small for statistical analysis, we noted that AIS B and C patient without elicitable MEPs had zero AIS improvement as compared to a mean improvement of greater than 1 (1.25) AIS grade in AIS B and C patients with elicitable MEPs.

In addition to the intraoperative MEPs, MRI prior to decompression surgery using the BASIC score distinguished AIS at discharge grade (Kruskal–Wallis test, $P < .001$). Further, a correlation between MEP status and MRI findings was observed as patients with absent MEPs had significantly higher BASIC scores in comparison to the patients with present MEPs (Spearman's rho = –0.667, $P < .001$). In the patients with preoperative MRI and no elicitable MEPs, 8/10 (80%) had a high BASIC score (ie, BASIC 3 or 4; Figure). All patients that had a BASIC score of 4 did not change in their AIS grade from admission to discharge. This is consistent with data in Talbott et al,[14] who noted a lack of improvement in patients who had higher BASIC scores, particularly BASIC 4 which is associated with intramedullary hemorrhage. Among patients with intact MEP and preoperative MRI, 16/17 (94%) had low BASIC scores with evidence of varying degrees of spinal cord sparing (ie, BASIC 0-2; Figure).[14,18]

DISCUSSION

Key Results

In the present study, we have evaluated the prognostic value of IOM for predicting early neurological recovery after acute SCI. Specifically, we show that intraoperative MEP status (ie, present or absent) is highly predictive of AIS grade and AIS conversion in severe SCI at time of patient discharge. Further, we show strong electroradiologic correlation, as intraoperative MEP status is highly correlated with axial MRI grade (BASIC score), a radiological measure that has been previously shown to highly correlate with early neurological impairment in SCI.[14,18]

Interpretation

Tsirikos and colleagues[19] published their experience with 80 patients with cervical, thoracic, and lumbar traumatic fractures, who underwent surgical reconstruction utilizing intraoperative SSEP monitoring. Approximately half of these patients had incomplete SCI associated with their fracture, although they did not further specify the severity of the injury or an AIS grade. They did note a direct relationship between the degree of SSEP amplitude depression during surgery and postoperative neurological worsening. Along the same lines, they demonstrated that an improvement of 20% or greater in amplitude was correlated with postoperative improvement. They did not report the use of MEPs in this series.

Castellon and colleagues[20] reported a small series of 18 patients with thoracolumbar burst fractures who underwent surgical reconstruction utilizing intraoperative SSEPs and MEPs. The majority of these patients were reported to be neurologically intact, and 4 patients had a mild SCI of AIS D or better. They noted a decrease in the mean latency after spinal cord decompression. They did not draw any conclusions regarding the relationship between MEPs and recovery from SCI. Curt et al[7] evaluated magnetic MEPs after SCI at the 25-d mark and found them to be significantly related to the outcome of ambulatory capacity and hand function.

Talbott and colleagues[14] recently published a 5-point MRI grading scale (BASIC score) based on axial T2 images for acute cervical and thoracic SCI.[18] We applied this scale to our patients and noted that patients with elicitable MEPs had significantly lower BASIC scores ($P < .001$). MEP status tended to segregate patients into 2 basic MRI patterns. A majority of patients (80%) without elicitable MEPs had T2 signal abnormality that involved the entire transverse extent of the spinal cord (BASIC 3 and 4), while nearly all patients (94%) with preserved MEPs had varying degrees of relative spinal cord sparing on axial T2 MRI (BASIC 0-2). These findings emphasize the importance of preserved spinal cord white matter for neurological function as now supported with both electrodiagnostic and imaging modalities in the current study. We also confirmed results from multiple prior studies related to the strong negative prognostic finding of intramedullary hemorrhage.[21,22] In our cohort, patients with evidence for intramedullary hemorrhage on axial T2 (BASIC 4) did not recover. None of these patients had elicitable MEPs. These findings represent an important and novel electroradiologic relationship between MRI and intraoperative MEP in acute traumatic SCI and highlight the value of a multimodality diagnostic approach.

To date, there have not been any published studies that have attempted to correlate MEPs, MRI grading, and recovery after SCI. Thus, these findings are important. For example, the use of MEP in spine trauma may also provide prognostic value that can guide postoperative treatment as well as patient/family counseling. Finally, the significant relationship between MEPs and neurological status/recovery and early MRI findings may lead to expanded use of MEPs outside of the operating room. MEPs may have a role in the intensive care unit setting, and perhaps may even be used to guide medical management, such as MAP goals. Future studies are required to evaluate the use of MEPs in the intensive care setting.

Limitations

The authors acknowledge that there are limitations to this study. This is a retrospective chart review, and is subject to the biases inherent with such studies. This study utilizes AIS grades rather than International standards for neurological classifications of SCI scores, which were only recently adopted at our institution. We acknowledge that AIS grades provide less detailed information to evaluate postsurgical changes. Our AIS grades were obtained during the acute hospitalization. Length of stay can be confounding for a variety of reasons, many of which are not a reflection of clinical outcomes. In our institution, a number of patients lack basic resources and health insurance, and often spend variable amounts of time admitted for social and placement issues. We understand that there is not a simple way to resolve the possible impact of this on our study, but we did confirm that there was not a relationship between presence of MEPs and length of stay. Documented bulbocavernosus reflex was not available for this review; however, we are collecting this data prospectively. While this study establishes MEPs as an important tool for SCI prognostication, it does not prove the superiority of using IOM during spine trauma surgery. In these patients, who often have highly unstable traumatic spine injuries, this modality may help the surgeon reduce the risk of iatrogenic injury during positioning, open/closed reduction, and surgical decompression. Finally, the most compelling finding in this study is the relationship between elicitable MEPs and SCI outcome. However, this is limited by a relatively small number of patients (32 patients), and a prospective study with more patients and fixed time points of outcome assessment is warranted. In spite of these limitations, this study has successfully identified a robust relationship between MEPs and neurological outcome after SCI.

CONCLUSION

Successful intraoperative elicitation of MEPs appears to be strongly associated with at least partial sparing of spinal cord tissue on axial T2 MRI and with neurological recovery after SCI. Future studies of the role MEPs in the ICU setting are warranted, and perhaps they may even be used to guide medical management, such as MAP goals. Our study is the first to demonstrate electroradiographic correlation between intraoperative electrophysiologic data (intraoperative MEP status) and previously validated MRI measures of injury severity in acute SCI. This study represents a novel and significant finding of a relationship between MEPs and potential for recovery after SCI during the acute hospitalization. Present data warrant more extensive evaluation in a prospectively designed multicenter study, and perhaps the expansion of the use of MEPs outside of the operating room in acute SCI.

Disclosures

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USING RNASEQ TO DISCOVER BLOOD BIOMARKERS FOR DIAGNOSIS OF SCI SEVERITY AND/OR PROGNOSIS OF NEUROLOGICAL RECOVERY: TRACK-SCI

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Spinal cord injury (SCI) is a devastating condition that dramatically alters the life of the patients who suffer from it. One major limitation of the SCI research field is that it still lacks a fluid biomarker which can be utilized i) towards assessing the initial severity of the injury which is a major factor in determining the downstream course of action and/or ii) for predicting the long term neurological recovery of the patient. In the era of high throughput technologies though, this poses a challenge that can be tackled with high confidence. Attempts to discover a biomarker in SCI, especially blood or cerebrospinal fluid (CSF), have met with limited success. In SCI it has been shown that the Central Nervous System (CNS) and the periphery are in constant communication. The systemic inflammatory response has been reported to be significantly affected by CNS injury both at the cellular and molecular level. Thus, we hypothesized that peripheral blood monocytes (PBMCs) will bear in their molecular signature important information about the severity and progression of the SCI. We seek this “encrypted” information as a liquid biopsy utilizing the high throughput RNAseq technology. To this end, as a part of our clinical study we have enrolled 59 SCI patients at the Zuckerberg San Francisco General Hospital and Trauma Center. After enrollment, peripheral blood is drawn and total RNA is extracted from PBMCs at multiple time points. Patients voluntarily donate blood to this study at 6 and 12 months post SCI as well. In addition to the PBMC RNA samples we collect a wide array of clinical data from these patients including MRIs, AIS garde and ISNCSCI scores for assessing motor and sensory functions. We used the RNAseq technology in a pilot study (3 samples from non-SCI individuals and 5 from SCI patients) to test the feasibility of the method. Our preliminary data revealed 973 genes which are differentially expressed between controls and SCI patients. In this dataset we identified genes which are traditionally implicated in trauma as well as genes which have never been studied in the SCI context. In addition, we identified 39 transcripts which display alternative splicing between controls and SCI patients as well as gene ontologies and pathways which were significantly enriched. We will present our preliminary RNAseq data analysis which will include data from 10 controls and 25 patients at that time as well as our future plans (both experimental and analytical) in isolating one or more reproducible diagnostic and/or prognostic biomarker(s) from our transcriptomic dataset. (supported by CDMRP SC150198)